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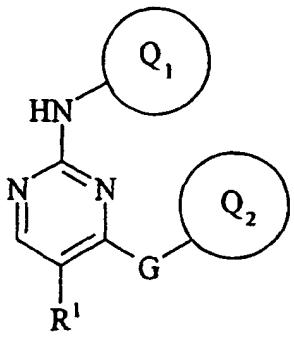
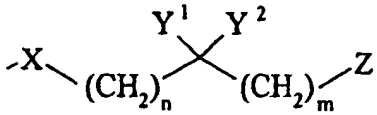


(I)



(Ia)

(57) Abstract: Pyrimidine derivatives of the formula (I) wherein: one of Q_1 and Q_2 or both of Q_1 and Q_2 is substituted on a ring carbon by one substituent of the formula (Ia) [provided that when present in Q_1 the substituent of formula (Ia) is not adjacent to the - NH- link]; wherein Q_1, Q_2, G, R^1, X, Y^1, Y^2, Z, n and m are as described within; and pharmaceutically acceptable salts and *in vivo* hydrolysable esters thereof are described. Processes for their manufacture, pharmaceutical compositions and their use as cyclin-dependent serine/threonine kinase (CDK) and focal adhesion kinase (FAK) inhibitors are also described.

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PYRIMIDINE COMPOUNDS

The invention relates to pyrimidine derivatives, or pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof, which possess cell-cycle inhibitory activity and are accordingly useful for their anti-cancer (such as anti-cell-proliferative, anti-cell migration and/or apoptotic) activity and are therefore useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of said pyrimidine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments or use in the production of an anti-cancer (anti-cell-proliferation/migration and/or apoptotic) effect in a warm-blooded animal such as man.

A family of intracellular proteins called cyclins play a central role in the cell cycle. The synthesis and degradation of cyclins is tightly controlled such that their level of expression fluctuates during the cell cycle. Cyclins bind to cyclin-dependent serine/threonine kinases (CDKs) and this association is essential for CDK (such as CDK1, CDK2, CDK4 and/or CDK6) activity within the cell. Although the precise details of how each of these factors combine to regulate CDK activity is poorly understood, the balance between the two dictates whether or not the cell will progress through the cell cycle.

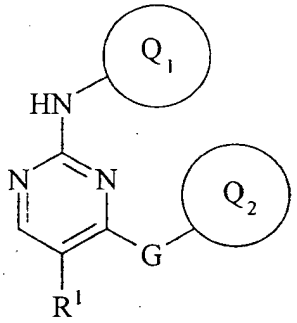
The recent convergence of oncogene and tumour suppresser gene research has identified regulation of entry into the cell cycle as a key control point of mitogenesis in tumours. Moreover, CDKs appear to be downstream of a number of oncogene signalling pathways. Disregulation of CDK activity by upregulation of cyclins and/or deletion of endogenous inhibitors appears to be an important axis between mitogenic signalling pathways and proliferation of tumour cells.

Accordingly it has been recognised that an inhibitor of cell cycle kinases, particularly inhibitors of CDK2, CDK4 and/or CDK6 (which operate at the S-phase, G1-S and G1-S phase respectively) should be of value as a selective inhibitor of cell proliferation, such as growth of mammalian cancer cells.

Furthermore, it is believed that inhibition of focal adhesion kinase (FAK), which is involved in signal transduction pathways, induces apoptosis (cell-death) and/or inhibits cell migration and an inhibitor of FAK may therefore have value as an anti-cancer agent.

The present invention is based on the discovery that certain 2,4-pyrimidine compounds surprisingly inhibit the effects of cell cycle kinases showing selectivity for CDK2, CDK4 and CDK6, and also inhibit FAK and thus possess anti-cancer (anti-cell-migration/proliferation and/or apoptotic) properties. Such properties are expected to be of value in the treatment of disease states associated with aberrant cell cycles and cell proliferation such as cancers (solid tumours and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

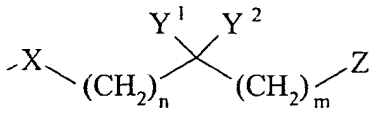
According to the invention there is provided a pyrimidine derivative of the formula **(I)**:



(I)

wherein:

$\mathbf{Q_1}$ and $\mathbf{Q_2}$ are independently selected from aryl or carbon linked heteroaryl; and one of Q_1 and Q_2 or both of Q_1 and Q_2 is substituted on a ring carbon by one substituent of the formula **(Ia)**:



(Ia)

[provided that when present in Q_1 the substituent of formula **(Ia)** is not adjacent to the -NH- link];

wherein:

X is $-CH_2-$, -O-, -NH-, $-NR^a-$ or -S- [wherein R^a is C_{1-4}alkyl, optionally substituted by one substituent selected from halo, amino, cyano, C_{1-4}alkoxy or hydroxy];

$\mathbf{Y^1}$ is H, C_{1-4}alkyl or as defined for Z;

Y^2 is H or C_{1-4}alkyl;

Z is R^bO-, R^cR^dN-, R^eS-, $R^fR^gNNR^h$-, a nitrogen linked heteroaryl or a nitrogen linked heterocycle [wherein said heterocycle is optionally substituted on a ring carbon or a ring nitrogen by C_{1-4}alkyl or C_{1-4}alkanoyl] wherein R^b, R^c, R^d, R^e, R^f, R^g and R^h are independently selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{3-8}cycloalkyl, and wherein said C_{1-4}alkyl and C_{2-4}alkenyl are optionally substituted by one or more phenyl;

n is 1, 2 or 3;

m is 1, 2 or 3;

G is -O- or -S-;

R^1 is selected from hydrogen, halo, hydroxy, nitro, amino, *N*-(C_{1-3}alkyl)amino, *N*,*N*-di-(C_{1-3}alkyl)amino, cyano, trifluoromethyl, trichloromethyl, C_{1-3}alkyl [optionally substituted by 1 or 2 substituents independently selected from halo, cyano, amino, *N*-(C_{1-3}alkyl)amino, *N*,*N*-di-(C_{1-3}alkyl)amino, hydroxy and trifluoromethyl], C_{3-5}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{3-5}alkynyl, C_{1-3}alkoxy, mercapto, C_{1-3}alkylsulphanyl, carboxy and C_{1-3}alkoxycarbonyl;

Q_1 is optionally substituted on a ring carbon by one to four substituents independently selected from halo, mercapto, nitro, formyl, formamido, carboxy, cyano, amino, ureido, carbamoyl, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl [wherein said C_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl are optionally substituted by one or more groups selected from R^i], C_{1-4}alkanoyl, C_{1-4}alkoxycarbonyl, heterocyclic group, C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2 [optionally substituted by hydroxy], *N*'-(C_{1-4}alkyl)ureido, *N*',*N*'-di-(C_{1-4}alkyl)ureido, *N*'-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N*',*N*'-di-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N*-C_{1-4}alkylamino, *N*,*N*-di-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N*,*N*-di-(C_{1-4}alkyl)sulphamoyl, *N*-C_{1-4}alkylcarbamoyl, *N*,*N*-di-(C_{1-4}alkyl)carbamoyl and C_{1-4}alkanoylamino;

and also independently, or in addition to, the above substituents, Q_1 may be optionally substituted by one to two substituents independently selected from aryl, C_{3-8}cycloalkyl and a heterocyclic group; wherein said aryl, C_{3-8}cycloalkyl or heterocyclic group may be optionally substituted on a ring carbon by one or more groups selected from R^j; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^k;

Q_2 is optionally substituted on a ring carbon by one to four substituents independently selected from halo, hydroxy, mercapto, nitro, formyl, formamido, carboxy, cyano, amino,

ureido, carbamoyl, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy [wherein said C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl and C_{1-4}alkoxy are optionally substituted by one or more groups selected from R^l], C_{1-4}alkanoyl, C_{1-4}alkoxycarbonyl, heterocyclic group, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 [optionally substituted by hydroxy], *N*'-(C_{1-4}alkyl)ureido, *N'*,*N*'-di-(C_{1-4}alkyl)ureido, *N*'-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N'*,*N*'-di-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N*-C_{1-4}alkylamino, *N*,*N*-di-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N*,*N*-di-(C_{1-4}alkyl)sulphamoyl, *N*-C_{1-4}alkylcarbamoyl, *N*,*N*-di-(C_{1-4}alkyl)carbamoyl, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, C_{1-4}alkanoylamino and a group of formula **(Ia)** or **(Ia')** as depicted above;

and also independently, or in addition to, the above substituents, Q_2 may be optionally substituted by one to two substituents independently selected from aryl, C_{3-8}cycloalkyl or a heterocyclic group; wherein said aryl, C_{3-8}cycloalkyl or heterocyclic group may be optionally substituted on a ring carbon by one or more groups selected from R^m; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^n;

$\mathbf{R^i}$ and $\mathbf{R^l}$ are independently selected from hydroxy, halo, amino, cyano, formyl, formamido, carboxy, nitro, mercapto, carbamoyl, sulphamoyl, *N*-C_{1-4}alkylamino, *N*,*N*-di-(C_{1-4}alkyl)amino, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, *N*-C_{1-4}alkylcarbamoyl, *N*,*N*-di-(C_{1-4}alkyl)carbamoyl, C_{1-4}alkanoylamino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkylsulphonylamino, *N*-(C_{1-4}alkyl)sulphamoyl, *N*-(C_{1-4}alkyl)$_2$sulphamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N*-(C_{1-4}alkyl)$_2$carbamoyl, phenyl, phenylthio, phenoxy, C_{3-8}cycloalkyl and a heterocyclic group; wherein said phenyl, phenylthio, phenoxy, C_{3-8}cycloalkyl or heterocyclic group may be optionally substituted on a ring carbon by one or more groups selected from R^o; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^p;

$\mathbf{R^j}$, $\mathbf{R^m}$ and $\mathbf{R^o}$ are independently selected from hydroxy, halo, amino, cyano, formyl, formamido, carboxy, nitro, mercapto, carbamoyl, sulphamoyl, C_{1-4}alkyl [optionally substituted by one or more groups selected from halo, cyano, amino, *N*-C_{1-4}alkylamino, *N*,*N*-di-(C_{1-4}alkyl)amino or hydroxy], C_{2-4}alkenyl [optionally substituted by one or more groups selected from halo], C_{2-4}alkynyl, *N*-C_{1-4}alkylamino, *N*,*N*-di-(C_{1-4}alkyl)amino, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, C_{1-4}alkoxy [optionally substituted by one or more groups

selected from halo], C_{1-4}alkoxycarbonyl, *N*-C_{1-4}alkylcarbamoyl, *N*,*N*-di-(C_{1-4}alkyl)carbamoyl, C_{1-4}alkanoylamino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkylsulphonylamino, *N*-(C_{1-4}alkyl)sulphamoyl, *N*-(C_{1-4}alkyl)$_2$sulphamoyl, phenyl, C_{3-8}cycloalkyl and a heterocyclic group; and

$\mathbf{R^k}$, $\mathbf{R^n}$ and $\mathbf{R^p}$ are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N*,*N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

"Aryl" is a fully or partially unsaturated, mono or bicyclic carbon ring that contains 4-12 atoms. Preferably "aryl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. More preferably "aryl" is phenyl, naphthyl, tetralinyl or indanyl. Particularly "aryl" is phenyl, naphthyl or indanyl. More particularly "aryl" is phenyl.

A "carbon linked heteroaryl" is a fully unsaturated, 5- or 6- membered monocyclic ring or 9- or 10- membered bicyclic ring of which at least one atom is chosen from nitrogen, sulphur or oxygen. This ring is linked via a carbon atom to the -NH- (for Q_1) or G (for Q_2). Preferably "carbon linked heteroaryl" is furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, triazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, indolyl, quinolyl or benzimidazolyl. More preferably "carbon linked heteroaryl" is pyridyl, thiazolyl or pyrazolyl. Particularly "carbon linked heteroaryl" is pyridyl.

A "heterocyclic group" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)-, and a ring sulphur atom may be optionally oxidised to form S-oxide(s). Preferably a "heterocyclic group" is pyrrolidinyl, morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, isothiazolyl, indolyl, quinolyl, thienyl, furyl, 1,3-benzodioxolyl, thiadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrazolyl, pyrrolinyl, homopiperazinyl, tetrahydropyranyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, imidazo[1,2-a]pyridine or 3-aza-8-oxabicyclo[3,2,1]hexane. More preferably a "heterocyclic group" is pyrrolidinyl, morpholino, piperidyl, indolyl, thienyl, furyl, piperazinyl,

thiomorpholino, pyrazolyl, imidazolyl, 2-pyrrolidone, imidazo[1,2-a]pyridine or 3-aza-8-oxabicyclo[3,2,1]hexane.

A suitable value a "nitrogen linked heteroaryl" is a mono or bicyclic ring that has a degree of unsaturation, containing 4-12 atoms, at least one of which is selected from nitrogen, and optionally 1-3 further atoms are selected from nitrogen, sulphur or oxygen, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, and a ring sulphur and/or nitrogen atom may be optionally oxidised to form S-oxide(s) and/or an N-oxide. Suitably "nitrogen linked heteroaryl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. The nitrogen link results in a neutral compound being formed. Suitable values for "nitrogen linked heteroaryl" include imidazol-1-yl, pyrrolin-1-yl, imidazolin-1-yl, pyrazolin-1-yl, triazol-1-yl, indol-1-yl, isoindol-2-yl, indolin-1-yl, benzimidazol-1-yl, pyrrol-1-yl or pyrazol-1-yl. Preferably "nitrogen linked heteroaryl" is imidazol-1-yl.

A suitable value a "nitrogen linked heterocycle" is an unsaturated mono or bicyclic ring that contains 4-12 atoms, at least one of which is selected from nitrogen, and optionally 1-3 further atoms are selected from nitrogen, sulphur or oxygen, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, and a ring sulphur may be optionally oxidised to form S-oxide(s). Suitably "nitrogen linked heterocycle" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "nitrogen linked heterocycle" include pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, thiomorpholino, homopiperidin-y-l or homopiperazin-1-yl. Preferably a "nitrogen linked heterocycle" is pyrrolidin-1-yl, piperazin-1-yl or morpholino. More preferably a "nitrogen linked heterocycle" is pyrrolidin-1-yl or piperazin-1-yl.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms. "Halo" is fluoro, chloro, bromo and iodo.

Examples of **C_{2-4}alkenyl** are vinyl and allyl; examples of **C_{2-6}alkenyl** are C_{3-5}alkenyl, vinyl and allyl; an example of **C_{3-6}alkenyl** is allyl; an examples of **C_{3-6}alkynyl** are C_{3-5}alkynyl and propyn-2-yl; examples of **C_{2-4}alkynyl** are ethynyl and propyn-2-yl; examples of **C_{2-6}alkynyl** are ethynyl and propyn-2-yl; examples of **C_{1-4}alkanoyl** are acetyl and propionyl; examples of **C_{1-4}alkoxycarbonyl** are C_{1-3}alkoxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and *tert*-butoxycarbonyl; examples of **C_{1-4}alkylene** are methylene, ethylene

and propylene; examples of **C_{1-4}alkyl** are C_{1-3}alkyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl and *tert*-butyl; examples of **C_{1-6}alkyl** are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl and 3-methylbutyl; examples of **C_{1-4}alkoxy** are C_{1-3}alkoxy, methoxy, ethoxy, propoxy, isopropoxy and butoxy; an example of **C_{2-4}alkenyloxy** is allyloxy; an example of **C_{2-4}alkynyloxy** is propynyloxy; examples of **C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2** are C_{1-3}alkylsulphanyl, methylthio, ethylthio, propylthio, methylsulphinyl, ethylsulphinyl, propylsulphinyl, mesyl, ethylsulphonyl and propylsulphonyl; examples of ***N*-C_{1-4}alkylcarbamoyl** are *N*-methylcarbamoyl, *N*-ethylcarbamoyl and *N*-propylcarbamoyl; examples of ***N*,*N*-di-(C_{1-4}alkyl)-carbamoyl** are *N*,*N*-dimethylcarbamoyl, *N*-ethyl-*N*-methylcarbamoyl and *N*,*N*-diethylcarbamoyl; examples of ***N*-C_{1-4}alkylamino** are *N*-(C_{1-3}alkyl)amino, methylamino, ethylamino and propylamino; examples of ***N*,*N*-di-(C_{1-4}alkyl)amino** are *N*,*N*-di-(C_{1-3}alkyl)amino, dimethylamino, *N*-ethyl-*N*-methylamino, diethylamino, *N*-methyl-*N*-propylamino and dipropylamino; examples of **C_{1-4}alkanoylamino** are acetamido, propionamido and butyramido; examples of **C_{3-8}cycloalkyl** are cyclopropyl, cyclopentyl and cyclohexyl; examples of **C_{1-4}alkanoyl** are acetyl and propionyl; examples of **C_{1-4}alkanoyloxy** are acetyloxy and propionyloxy; examples of ***N'*-(C_{1-4}alkyl)ureido** are *N'*-methylureido and *N'*-ethylureido; examples of ***N',N'*-di-(C_{1-4}alkyl)ureido** are *N',N'*-dimethylureido, *N',N'*-diisopropylureido and *N'*-methyl-*N'*-propylureido; examples of ***N'*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido** are *N'*-methyl-*N*-ethylureido and *N'*-methyl-*N*-methylureido; examples of ***N',N'*-di-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido** are *N',N'*-dimethyl-*N*-ethylureido and *N'*-methyl-*N'*-propyl-*N*-butylureido; examples of ***N*-(C_{1-4}alkyl)sulphamoyl** are *N*-methylsulphamoyl and *N*-isopropylsulphamoyl; examples of ***N*,*N*-di-(C_{1-4}alkyl)sulphamoyl** are *N*-methyl-*N*-ethylsulphamoyl and *N*,*N*-dipropylsulphamoyl; and examples of **C_{1-4}alkylsulphonylamino** are mesylamino, ethylsulphonylamino and propylsulphonylamino.

A suitable pharmaceutically acceptable salt of a pyrimidine derivative of the invention is, for example, an acid-addition salt of a pyrimidine derivative of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a pyrimidine derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a

sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the formula **(I)** may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula **(I)**. Examples of pro-drugs include *in vivo* hydrolysable esters of a compound of the formula **(I)**.

An *in vivo* hydrolysable ester of a compound of the formula **(I)** containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula **(I)** containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

Some compounds of the formula **(I)** may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereo-isomers and geometric isomers that possess CDK and/or FAK inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula **(I)** that possess CDK and/or FAK inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess CDK and/or FAK inhibitory activity.

Particular preferred compounds of the invention comprise a pyrimidine derivative of the formula (I), or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, wherein R^1, Q_1, Q_2, and G have any of the meanings defined hereinbefore, or any of the following values. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Preferably Q_1 and Q_2 are independently selected from phenyl, pyridyl, thiazolyl and pyrazolyl.

More preferably Q_1 and Q_2 are independently selected from phenyl and thiazolyl.

In another aspect of the invention, more preferably Q_1 and Q_2 are independently selected from phenyl and thiazolyl.

Preferably Q_1 is phenyl.

Preferably Q_2 is phenyl, pyridyl, thiazolyl or pyrazolyl.

More preferably Q_2 is phenyl or thiazolyl.

In another aspect of the invention, more preferably Q_2 is phenyl or pyridyl.

Preferably Q_1 is phenyl and Q_2 is selected from phenyl, pyridyl, thiazolyl and pyrazolyl.

More preferably Q_1 is phenyl and Q_2 is selected from phenyl and thiazolyl.

In another aspect of the invention, more preferably Q_1 is phenyl and Q_2 is selected from phenyl and pyridyl.

Preferably in the substituent **(Ia)**, X is -O-, Y^1 is OH, Y^2 is H, Z is R^cR^dN- or a nitrogen linked heterocycle [wherein said heterocycle is optionally substituted on a ring nitrogen by C_{1-4}alkanoyl] and wherein R^c and R^d are independently selected from hydrogen, C_{1-4}alkyl and C_{3-8}cycloalkyl, n is 1 and m is 1.

More preferably in the substituent **(Ia)** X is -O-, Y^1 is OH, Y^2 is H, Z is amino, methylamino, ethylamino, isopropylamino, isobutylamino, *t*-butylamino, dimethylamino, cyclopentylamino, pyrrolidin-1-yl or 4-acetylpiperazin-1-yl, n is 1 and m is 1.

Particularly the substituent **(Ia)** is 3-amino-2-hydroxypropoxy, 3-methylamino-2-hydroxypropoxy, 3-dimethylamino-2-hydroxypropoxy,

3-ethylamino-2-hydroxypropoxy, 3-isopropylamino-2-hydroxypropoxy, 3-isobutylamino-2-hydroxypropoxy, 3-*t*-butylamino-2-hydroxypropoxy, 3-(4-acetylpiperazin-1-yl)-2-hydroxypropoxy, 3-cyclopentylamino-2-hydroxypropoxy or 3-pyrrolidin-1-yl-2-hydroxypropoxy.

More particularly the substituent **(Ia)** is 3-dimethylamino-2-hydroxypropoxy, 3-isopropylamino-2-hydroxypropoxy, 3-*t*-butylamino-2-hydroxypropoxy or 3-cyclopentylamino-2-hydroxypropoxy.

Preferably the substituent of formula **(Ia)** is in ring Q_1.

Preferably when Q_1 is phenyl the substituent of formula **(Ia)** is in either the para- or meta- position relative to the -NH-.

More preferably when Q_1 is phenyl the substituent of formula **(Ia)** is in the para-position relative to the -NH-.

In one aspect of the invention preferably G is -O-.

In another aspect of the invention preferably G is -S-.

Preferably R^1 is fluoro, chloro or bromo.

More preferably R^1 bromo.

Preferably Q_1 is unsubstituted except by the substituent of formula **(Ia)**.

Preferably Q_2 is unsubstituted or substituted by one methoxy group.

Preferably Q_2 is phenyl, 4-methoxyphenyl or thiazol-2-yl.

Therefore, in a preferred aspect of the invention there is provided a pyrimidine derivative of the formula **(I)** as depicted above, wherein:

Q_1 and Q_2 are independently selected from phenyl and thiazolyl; Q_2 is unsubstituted or substituted by one methoxy group; and Q_1 is substituted on a ring carbon by a substituent of formula **(Ia)** as depicted above wherein X is -O-, Y^1 is OH, Y^2 is H, Z is R^cR^dN- or a nitrogen linked heterocycle [wherein said heterocycle is optionally substituted on a ring nitrogen by C_{1-4}alkanoyl] and wherein R^c and R^d are independently selected from hydrogen, C_{1-4}alkyl and C_{3-8}cycloalkyl, n is 1 and m is 1;

G is -O- or -S-; and

R^1 is fluoro, chloro or bromo;

or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

Therefore, in a more preferred aspect of the invention there is provided a pyrimidine derivative of the formula **(I)** as depicted above, wherein:

More preferably Q_1 is phenyl and Q_2 is selected from phenyl and thiazolyl; Q_2 is unsubstituted or substituted by one methoxy group; and Q_1 is substituted on a ring carbon by 3-amino-2-hydroxypropoxy, 3-methylamino-2-hydroxypropoxy, 3-dimethylamino-2-hydroxypropoxy, 3-ethylamino-2-hydroxypropoxy, 3-isopropylamino-2-hydroxypropoxy, 3-isobutylamino-2-hydroxypropoxy, 3-*t*-butylamino-2-hydroxypropoxy, 3-(4-acetylpiperazin-1-yl)-2-hydroxypropoxy, 3-cyclopentylamino-2-hydroxypropoxy or 3-pyrrolidin-1-yl-2-hydroxypropoxy;

G is -O- or -S-; and

R^1 is bromo;

or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

In one aspect of the invention preferred compounds of the invention are those of Examples 1, 6, 14, 15, 16 or 17 or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

In a further aspect of the invention preferred compounds of the invention include any one of the Examples or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

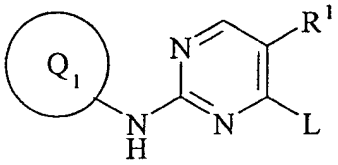
Preferred aspects of the invention are those which relate to the compound or a pharmaceutically acceptable salt thereof.

A pyrimidine derivative of the formula **(I)**, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a pyrimidine derivative of the formula **(I)**, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, are provided as a further feature of the invention and are illustrated by the following representative examples in which, unless otherwise stated R^1, Q_1, Q_2 and G have any of the meanings defined hereinbefore for a pyrimidine derivative of the formula **(I)** and unless another substituent is drawn on ring Q_1 or Q_2 the ring may bear any of the substituents described hereinbefore (optionally protected as necessary). Where a substituent is drawn on ring Q_1, this includes (unless stated otherwise) the possibilities of the substituent being on ring Q_2 in addition to, or instead of the substituent being on ring Q_1. Necessary starting materials may be obtained by standard procedures of organic chemistry (see for example, Advanced Organic Chemistry (Wiley-Interscience), Jerry March - also useful for general guidance on reaction conditions and reagents). The preparation of such starting materials is described within the accompanying non-limiting processes and Examples.

Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

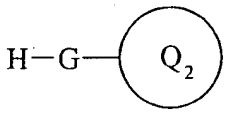
Thus, as a further feature of the invention there are provided the following processes which comprises of:-

a) for compounds of formula **(I)**; reacting a pyrimidine of formula **(II)**:



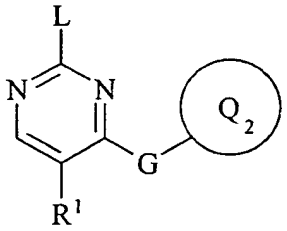
(II)

wherein L is a displaceable group as defined below, with a compound of formula **(III)**:



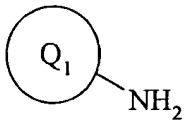
(III)

b) reaction of a pyrimidine of formula **(IV)**:



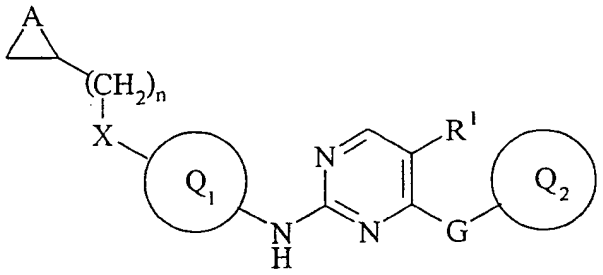
(IV)

wherein L is a displaceable group as defined below, with a compound of formula **(V)**:



(V)

c) for compounds of formula **(I)** where n is 1, 2 or 3, m = 1, Y^2 is H and Y^1 is OH, NH_2 or SH; by reaction of a 3-membered heteroalkyl ring of formula **(VI)**:



(VI)

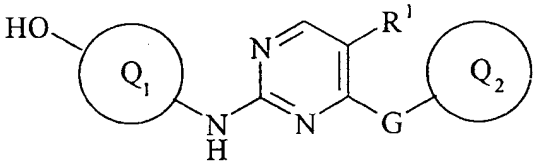
wherein A is O, S or NH; with a nucleophile of formula **(VII)**:

Z-D

(VII)

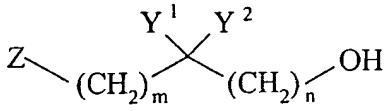
wherein D is H or a suitable counter-ion;

d) for compounds of formula **(I)** where X is oxygen; by reaction of an alcohol of formula **(VIII)**:



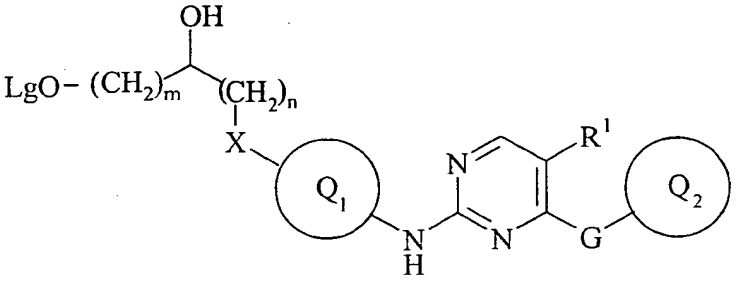
(VIII)

with an alcohol of formula **(IX)**:



(IX)

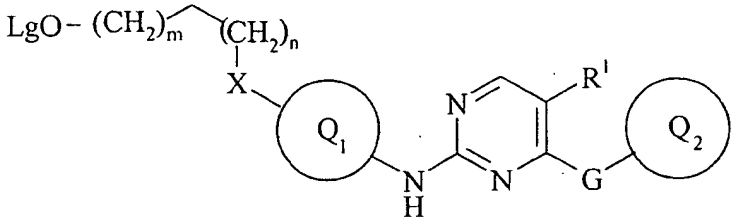
e) for compounds of formula **(I)** wherein X is $-CH_2-$, -O-, -NH- or -S-, Y^1 is OH, Y^2 is H and m is 2 or 3; reaction of a compound of formula **(X)**:



(X)

wherein LgO is a leaving group as defined below; with a nucleophile of formula **(VII)**;

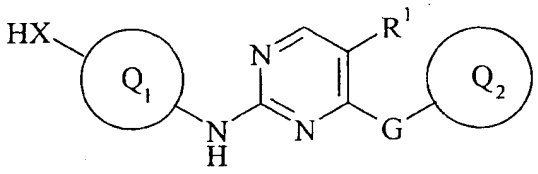
f) for compounds of formula **(I)** wherein X is $-CH_2-$, -O-, -NH- or -S-; Y^1 and Y^2 are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula **(XI)**:



(XI)

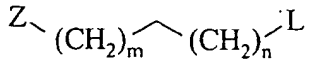
wherein LgO is a leaving group as defined below; with a nucleophile of formula **(VII)**;

g) for compounds of formula **(I)** wherein X is -O-, -NH- or -S-; Y^1 and Y^2 are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula **(XII)**:



(XII)

with a compound of formula **(XIII)**



(XIII)

wherein L is a displaceable group as defined below;

h) for compounds of formula **(I)** in which Z is HS-, by conversion of a thioacetate group in a corresponding compound;

and thereafter if necessary:

i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

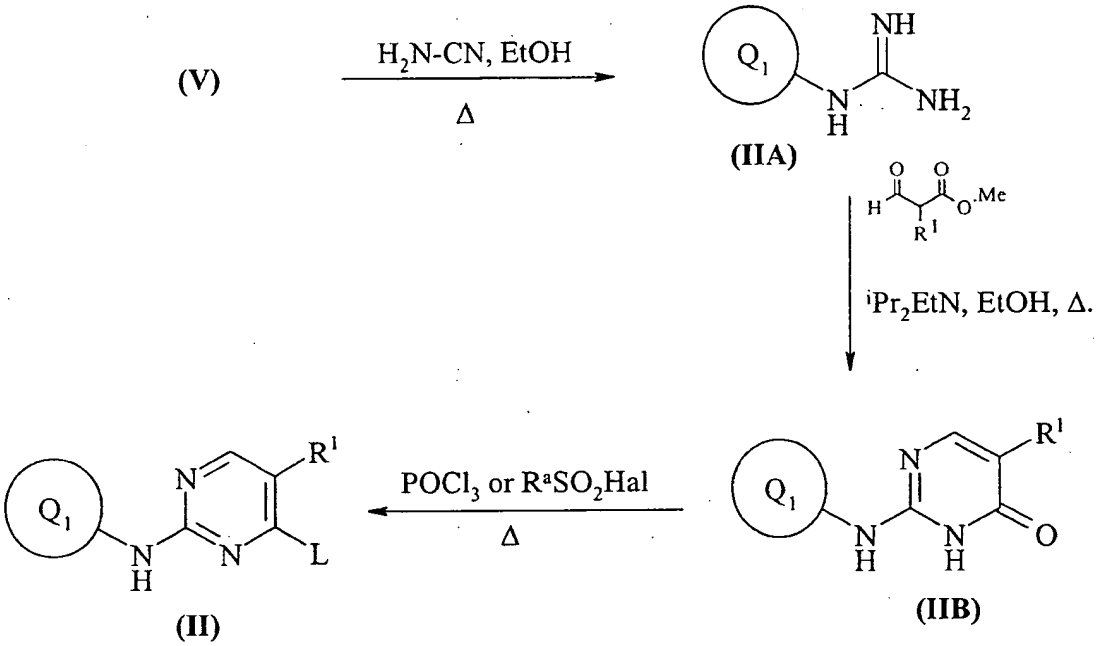
L is a displaceable group, suitable values for L are for example, a halo, sulphonyloxy or sulphur group, for example a chloro, bromo, methanesulphonyloxy, toluene-4-sulphonyloxy, mesyl, methylthio and methylsulphinyl.

Specific reaction conditions for the above reactions are as follows:-

Process a)

Pyrimidines of formula **(II)** and compounds of formula **(III)** may be reacted together, optionally in the presence of a suitable base, for example an inorganic base such as potassium carbonate. The reaction is preferably carried out in a suitable inert solvent or diluent, for example dichloromethane (DCM), acetonitrile, butanol, tetramethylene sulphone, tetrahydrofuran, 1,2-dimethoxyethane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide or *N*-methylpyrrolidin-2-one, and at a temperature in the range, for example, 0° to 150°C, conveniently at or near ambient temperature.

Pyrimidines of the formula **(II)** may be prepared according to the following scheme:



wherein R^a is an optionally substituted alkyl or aryl group and L is a displaceable group as defined above. Preferably R^a is methyl, ethyl or p-tolyl.

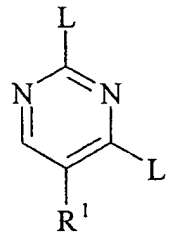
Compounds of formula **(III)** are commercially available or are prepared by processes known in the art.

Process b)

Pyrimidines of formula **(IV)** and anilines of formula **(V)** may be reacted together, i) in the presence of a suitable solvent for example a ketone such as acetone or an alcohol such as ethanol or butanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolidine, optionally in the presence of a suitable acid such as those defined above (or a suitable Lewis acid) and at a temperature in the range of 0°C to reflux, preferably reflux; or

ii) under standard Buchwald conditions as described above.

Pyrimidines of formula **(IV)** are prepared according to the following scheme:



(IVA) + **(III)** → (1) $^{i}Pr_2EtN$, BuOH, Δ ; or (2) Buchwald conditions → **(IV)**

wherein L is a displaceable group as defined above.

The anilines of formula **(V)** are commercially available or are prepared by processes known in the art.

Pyrimidines of the formula **(IVA)** are commercially available or may be prepared by, for example, reacting a compound of formula **(IVA)** in which L is -OH (i.e. a uracil), with $POCl_3$ to give a compound of formula **(IVA)** in which L is -Cl.

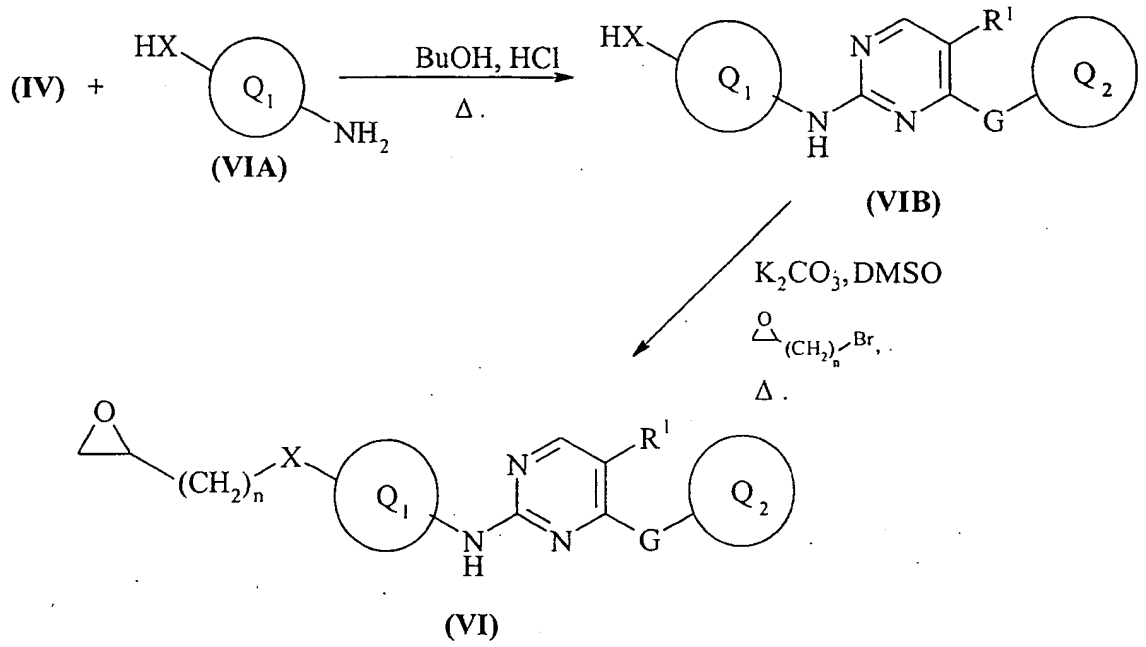
Process c)

Three membered heteroalkyl rings of formula **(VI)** and nucleophiles of formula **(VII)** are reacted together at a temperature in the range of 20° to 100°C, preferably 20° to 50°C, optionally in the presence of a suitable solvent, for example *N*,*N*-dimethylformamide, dimethyl sulphoxide or tetrahydrofuran.

Compounds formula **(VI)** may be prepared according to the following schemes:

Scheme I):

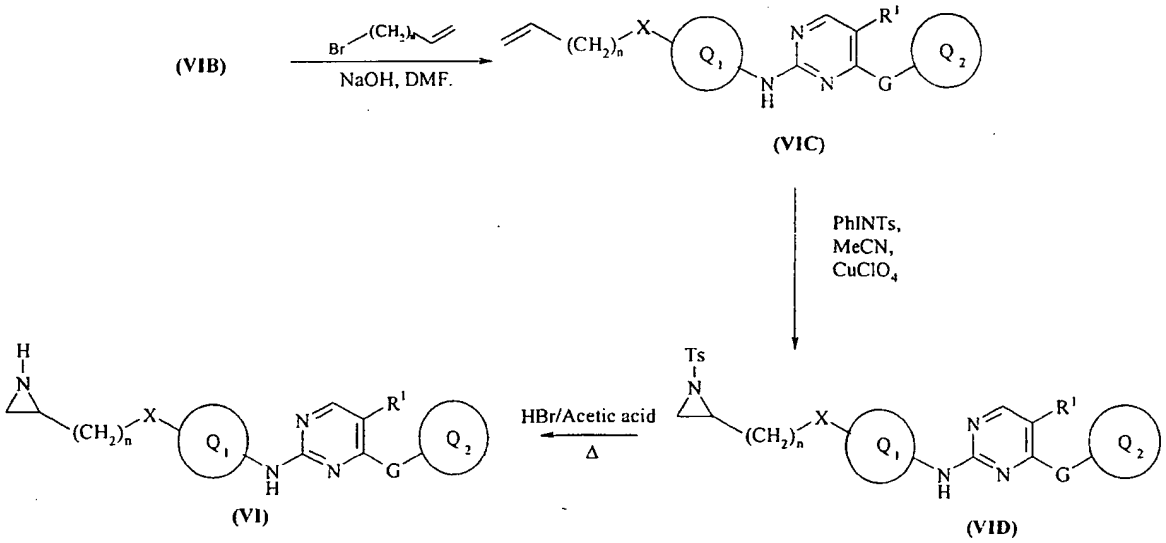
For compounds of formula **(VI)** where A is O, and X is not carbon:



The conversion of **(VIB)** to **(VI)** may also be achieved by reaction with Br-$(CH_2)_n$-CHO, or an equivalent ester, in DMF and the presence of a base, followed by reaction with a sulphur ylide such as (Me_2SOCH_2) in an inert solvent such as THF (see scheme V).

Scheme II):

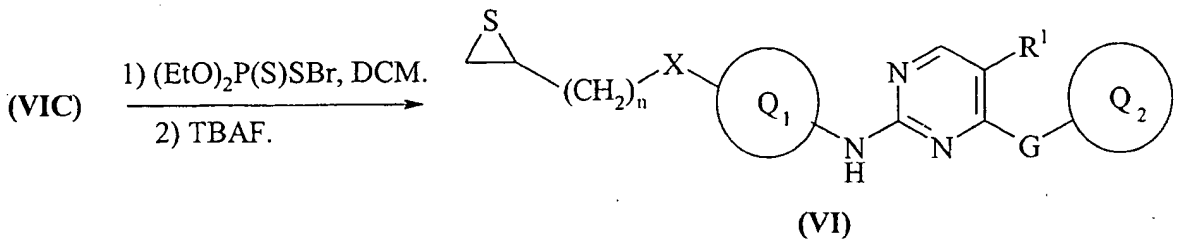
For compounds of formula **(VI)** where A is NH, and X is not carbon:



(for PhINTs see, for example, Tet. Let., 1997, 38 (39), 6897-6900; compounds of formula **(VIC)** may also be oxidised to the epoxide using conditions similar to that in Scheme IV) below);

Scheme III):

For compounds of formula **(VI)** where A is S, and X is not carbon:

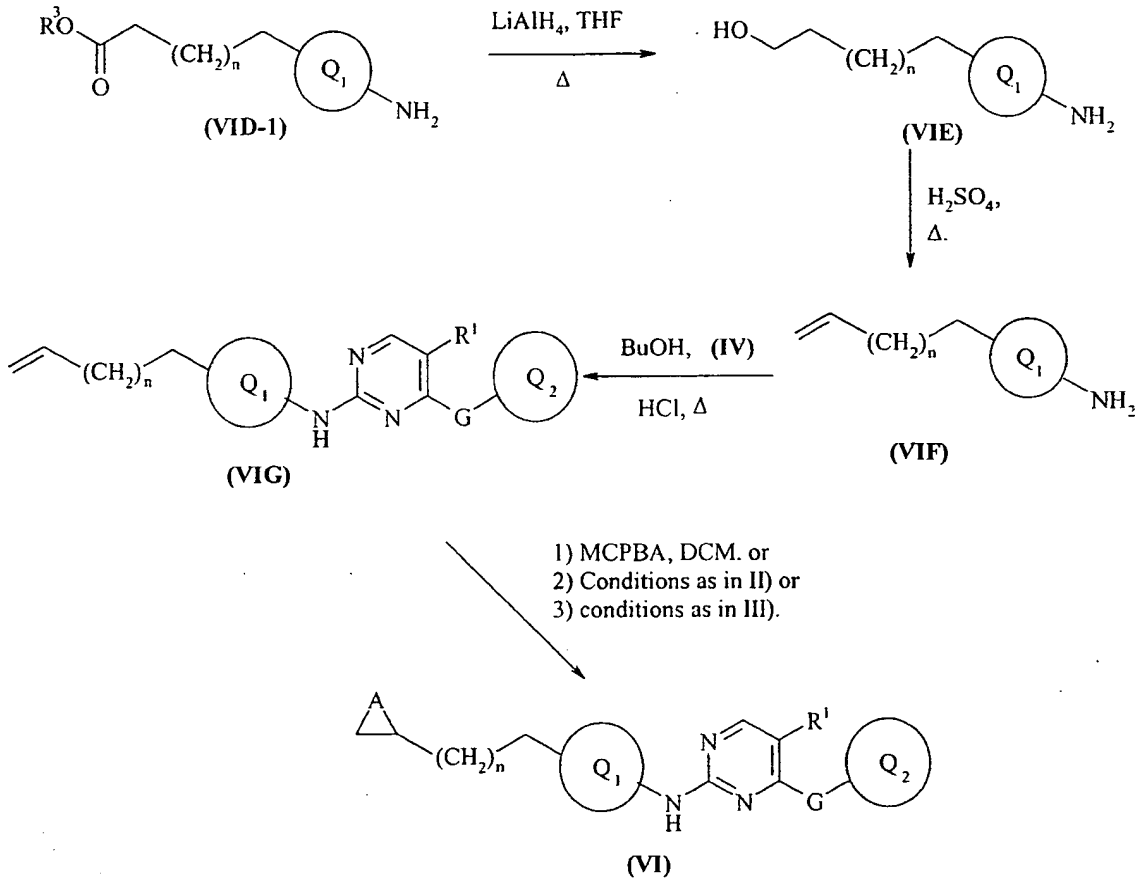


(VI)

(for example see *Synlett*, 1994, 267-268);

Scheme IV):

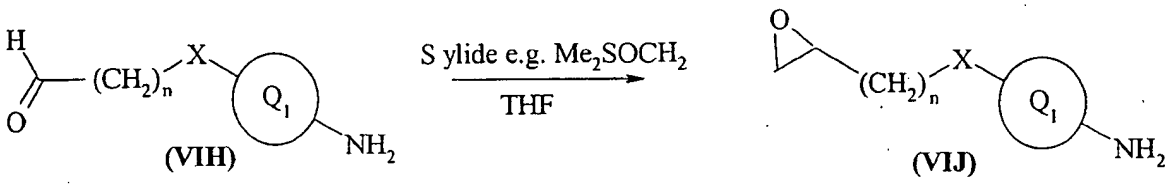
For compounds of formula **(VI)** where X is carbon



wherein R^3 together with the -COO- group to which it is attached forms an ester moiety, for example a methyl ester or an ethyl ester.

Scheme V)

For compounds of formula **(VI)** wherein X is CH_2, O, NH or S; Y^1 is OH; Y^2 is H; n is 1, 2 or 3 and m is 1 :



(VIJ) is reacted with **(IV)** (see Scheme I) to give **(VI)**.

An equivalent ester of **(VIH)** may also be used. See also Russ. Chem. Rev. 47, 975-990, 1978.

Compounds of formula **(VIH)**, **(VII)**, **(VIA)** and **(VID-1)** are commercially available or are prepared by processes known in the art.

Process d)

Alcohols (e.g. phenols) of formula **(VIII)** and alcohols of formula **(IX)** can be reacted together under standard Mitsunobu conditions. For example in the presence of diethyl azodicarboxylate and triphenyl phosphine, in a suitable solvent such as dichloromethane, toluene or tetrahydrofuran, and at a temperature in the range of 0 to 80°C, preferably in the range of 20 to 60°C. Alternatively, alcohols (phenols) of formula **(VIII)** may be alkylated with a suitable compound of formula **(IX)** in which the terminal hydroxy group has been replaced by a suitable leaving group.

Alcohols of formula **(VIII)** are made according to the process in I) above for the synthesis of intermediate **(VIB)** (where X is oxygen).

Alcohols of formula **(IX)** are commercially available or are made by processes known in the art.

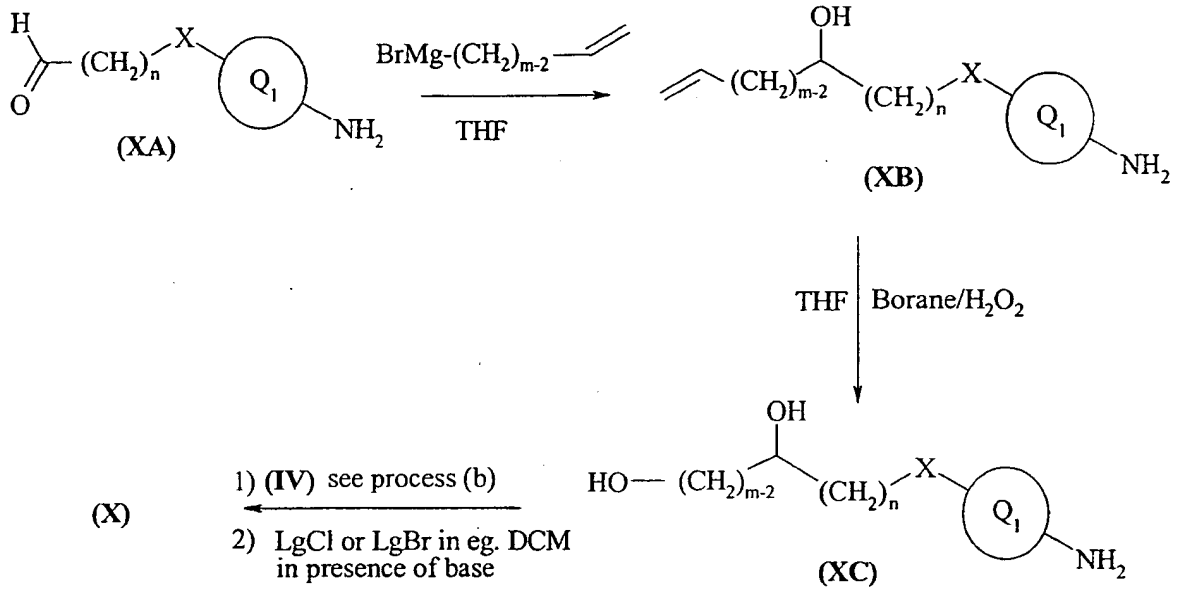
In a process analogous to process d), compounds in which X is -S- may be prepared by reaction of a compound of formula **(VIII)** in which the hydroxy group is -SH, with a compound of formula **(IX)** in which the hydroxy group is a leaving group such as mesylate or tosylate.

Process e)

Compounds of formula **(X)** wherein X is $-CH_2-$, -O-, -NH- or -S-; Y^1 is OH, Y^2 is H and m is 2 or 3 and nucleophiles of formula **(VII)** are reacted together at a temperature in the range of 20° to 100°C, preferably 20° to 50°C, optionally in the presence of a suitable solvent,

for example *N,N*-dimethylformamide, dimethyl sulphoxide or tetrahydrofuran, and optionally in the presence of a suitable base, such as potassium carbonate.

Compounds of formula **(X)** are prepared according to the following scheme (m is 2 or 3):



The order of steps 1) and 2) in the final step may be reversed. A suitable base for step 2) is triethylamine.

Compounds of formula **(XA)** and **(VII)** are commercially available or are prepared by processes known in the art. For example, compounds of formula **(XA)** in which X is -NH-, -O- or -S- may be prepared by reaction of a compound of formula **(VIA)** with a suitable haloaldehyde or equivalent ester under standard conditions for such reactions.

Process f)

Compounds of formula **(XI)** and nucleophiles of formula **(VII)** are reacted together as described for process e) above.

Compounds of formula **(XI)** are prepared in an analogous manner to step 2) in the final step of the process for preparing compounds of formula **(X)** above. The necessary primary alcohol starting materials are commercially available or are prepared by processes known in the art.

Process g)

Compounds of formula **(XII)** and **(XIII)** are reacted in an inert solvent such as DMF in the presence of a base such as potassium carbonate.

Compounds of formula **(XII)** are of the same generic formula as compounds of formula **(VIB)** described herein and are prepared as described for those compounds (see Scheme I). Compounds of formula **(XIII)** are commercially available or are prepared by processes known in the art.

Process h)

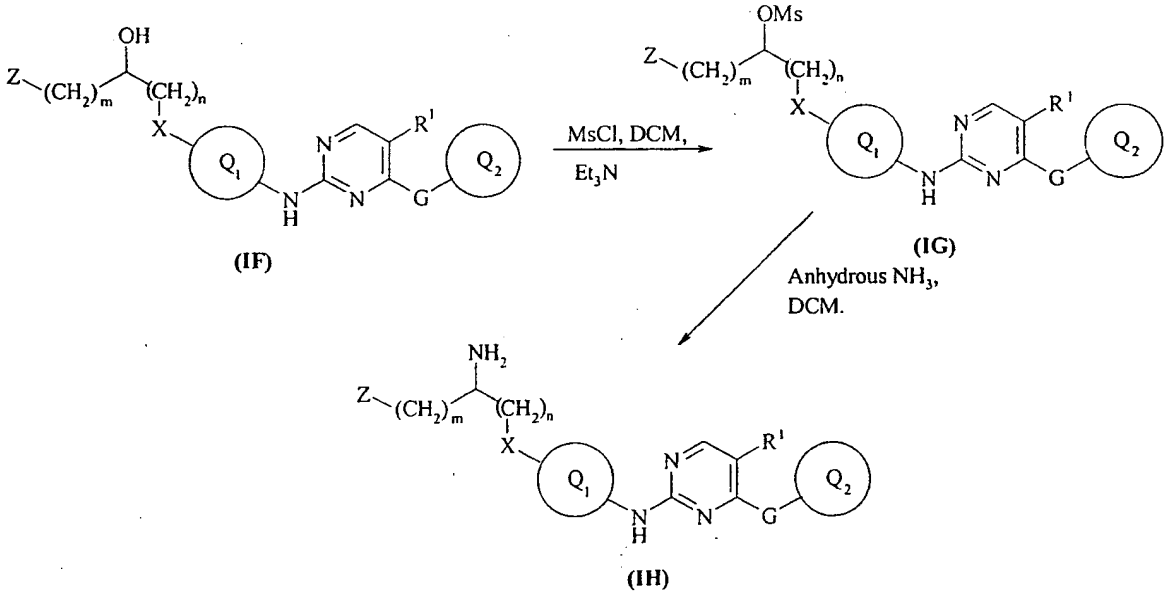
For the compounds of formula **(I)** in which Z is SH, the conversion of a thioacetate group in a corresponding compound is carried out as described herein for the conversion of compounds of formula **(IJ)** into **(IK)**.

Suitable starting materials containing a thioacetate group are prepared from corresponding compounds containing a leaving group such as mesylate or tosylate (prepared using standard conditions from the corresponding hydroxy compound) using thiol acetic acid as described herein for the conversion of compounds of formula **(IG)** into **(IJ)**.

Examples of conversions of a compound of formula **(I)** into another compound of formula **(I)** are:

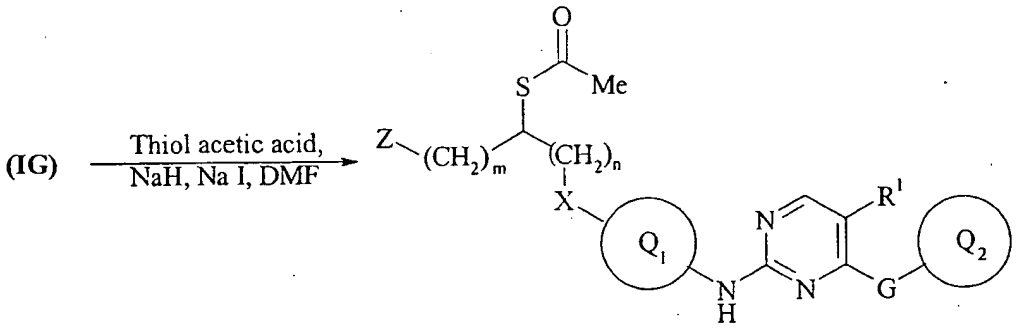
i) conversion of one side chain of formula **(Ia)** into another side chain of formula **(Ia)**; for example:

I) for compounds of formula **(I)** where Y^2 is H and Y^1 is not hydroxy (this reaction is depicted using ammonia):

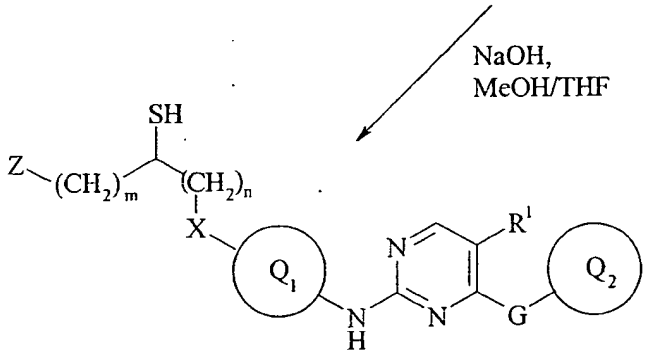


or:

II) for compounds of formula **(I)** where Y^2 is H and Y^1 is S:

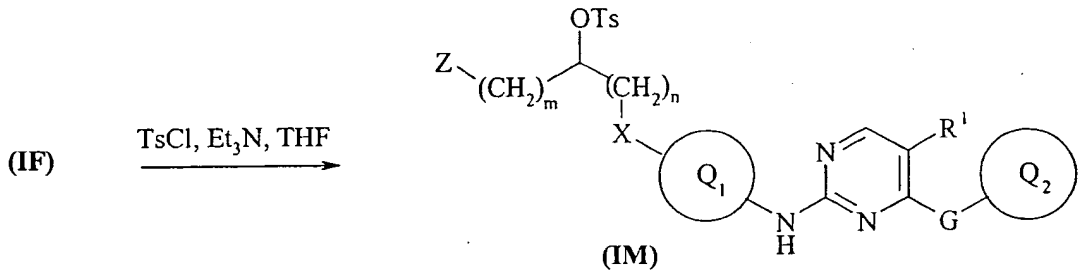


(IJ)

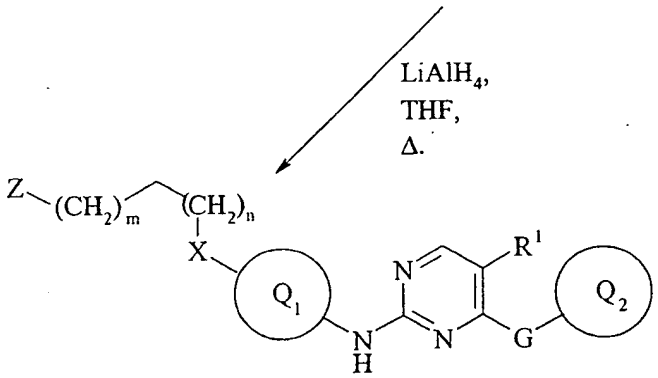


(IK)

III) for compounds of formula **(I)** where Y^2 is H and Y^1 is H:



(IM)

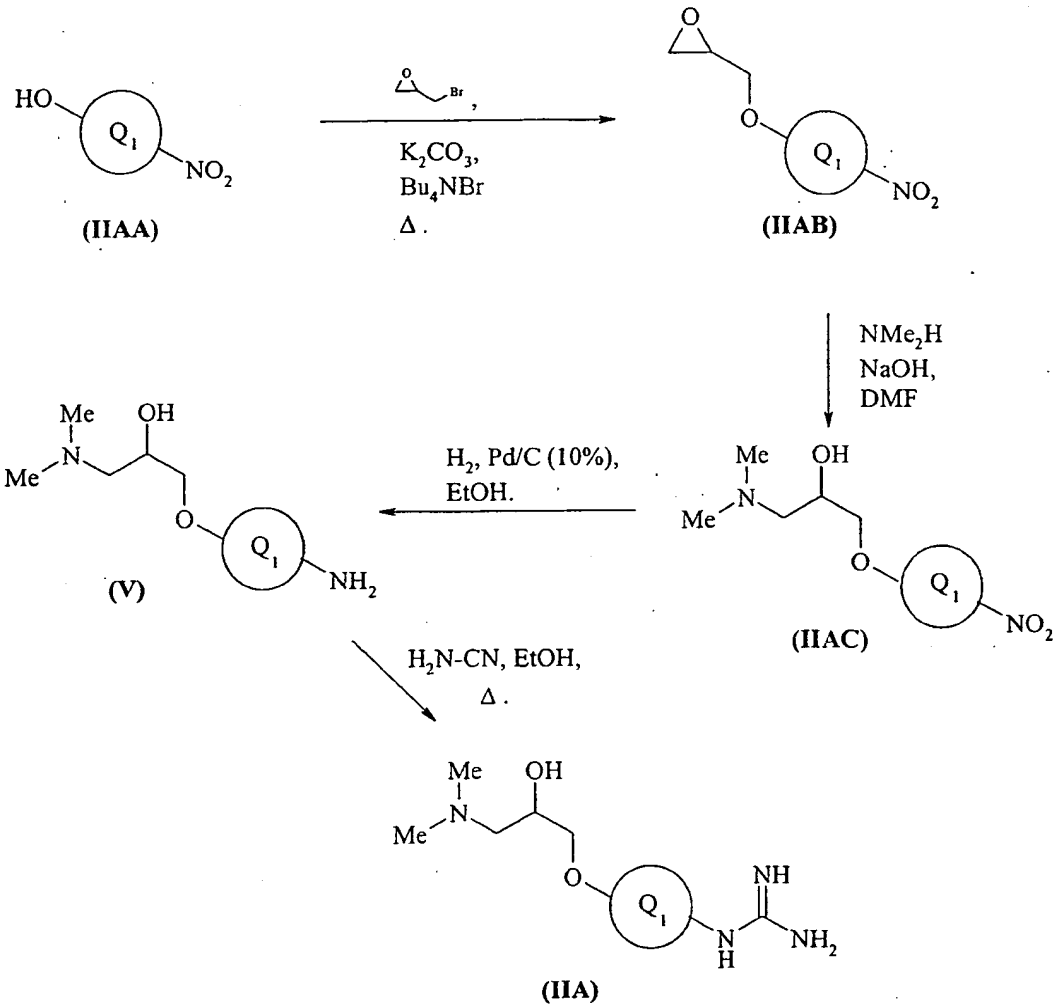


(IP)

It will be appreciated that these reactions are also suitable for conversion of one side chain of formula **(Ia)** into another side chain of formula **(Ia)**.

ii) conversion of one value of R^1 into another value of R^1, using standard techniques, for example, conversion of R^1 as hydroxy into C_{1-4}alkoxy.

The skilled reader will appreciate that the manipulation of the side chain **(Ia)** described in Processes c), d), e), f), g) and h) and i) above may also be performed on intermediates for example to make intermediates of formula **(II)**, **(IIA)**, **(IIB)**, or **(V)**. For example:



A preferred process of the invention is Process b).

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a

substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halo group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group

for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Many of the intermediates defined herein are novel, for example, those of the formula II and IV and these are provided as a further feature of the invention.

ASSAYS

As stated hereinbefore the pyrimidine derivative defined in the present invention possesses anti-cell-proliferation activity such as anti-cancer activity which is believed to arise from the CDK and/or FAK inhibitory activity of the compound. These properties may be assessed, for example, using the procedure set out below:-

CDK4 Inhibition Assay

The following abbreviations have been used :-

HEPES is *N*-(2-Hydroxyethyl)piperazine-*N'*-(2-ethanesulfonic acid)

DTT is Dithiothretiol

PMSF is Phenylmethylsulfonyl fluoride

The compounds were tested in an i*n vitro* kinase assay in 96 well format using Scintillation Proximity Assay (SPA - obtained from Amersham) for measuring incorporation

of [γ-33-P]-Adenosine Triphosphate into a test substrate (GST-Retinoblastoma). In each well was placed the compound to be tested (diluted in DMSO and water to correct concentrations) and in control wells either p16 as an inhibitor control or DMSO as a positive control.

Approximately 0.5µl of CDK4/Cyclin D1 partially-purified enzyme (amount dependent on enzyme activity) diluted in 25µl incubation buffer was added to each well then 20µl of GST-Rb/ATP/ATP33 mixture (containing 0.5µg GST-Rb and 0.2µM ATP and 0.14µCi [γ-33-P]-Adenosine Triphosphate), and the resulting mixture shaken gently, then incubated at room temperature for 60 minutes.

To each well was then added 150µL stop solution containing (0.8mg/well of Protein A-PVT SPA bead (Amersham)), 20pM/well of Anti-Glutathione Transferase, Rabbit IgG (obtained from Molecular Probes), 61mM EDTA and 50mM HEPES pH 7.5 containing 0.05% sodium azide.

The plates were sealed with Topseal-S plate sealers, left for two hours then spun at 2500rpm, 1124xg., for 5 minutes. The plates were read on a Topcount for 30 seconds per well.

The incubation buffer used to dilute the enzyme and substrate mixes contained 50mM HEPES pH7.5, 10mM $MnCl_2$, 1mM DTT, 100µM Sodium vanadate, 100µM NaF, 10mM Sodium Glycerophosphate, BSA (1mg/ml final).

As a control, another known inhibitor of CDK4 may be used in place of p16.

Test substrate

In this assay only part of the retinoblastoma (Science 1987 Mar13;235(4794):1394-1399; Lee W.H., Bookstein R., Hong F., Young L.J., Shew J.Y., Lee E.Y.) was used, fused to a GST tag. PCR of retinoblastoma amino acids 379-928 (obtained from retinoblastoma plasmid ATCC pLRbRNL) was performed, and the sequence cloned into pGEX 2T fusion vector (Smith D.B. and Johnson, K.S. Gene 67; 31 (1988); which contained a tac promoter for inducible expression, internal lac I^q gene for use in any E.Coli host, and a coding region for thrombin cleavage - obtained from Pharmacia Biotech) which was used to amplify amino acids 792-928. This sequence was again cloned into pGEX 2T.

The retinoblastoma 792-928 sequence so obtained was expressed in E.Coli (BL21 (DE3) pLysS cells) using standard inducible expression techniques, and purified as follows.

E.coli paste was resuspended in 10ml/g of NETN buffer (50mM Tris pH 7.5, 120mM NaCl, 1mM EDTA, 0.5%v/v NP-40, 1mM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) and sonicated for 2 x 45 seconds per 100ml homogenate. After

centrifugation, the supernatant was loaded onto a 10ml glutathione Sepharose column (Pharmacia Biotech, Herts, UK), and washed with NETN buffer. After washing with kinase buffer (50mM HEPES pH 7.5, 10mM MgCl2, 1mM DTT, imM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) the protein was eluted with 50mM reduced glutathione in kinase buffer. Fractions containing GST-Rb(792-927) were pooled and dialysed overnight against kinase buffer. The final product was analysed by Sodium Dodeca Sulfate (SDS) PAGE (Polyacrylamide gel) using 8-16% Tris-Glycine gels (Novex, San Diego, USA).

CDK4 and Cyclin D1

CDK4 and Cyclin D1 were cloned from RNA from MCF-7 cell line (obtained from ATCC number:HTB22, breast adenocarcinoma line) as follows. The RNA was prepared from MCF-7 cells, then reverse transcribed using oligo dT primers. PCR was used to amplify the complete coding sequence of each gene [CDK4 amino acids 1-303; Ref. Cell 1992 Oct 16; 71(2): 323-334; Matsushime H., Ewen M.E., Stron D.K., Kato J.Y., Hanks S.K., Roussel M.F., Sherr C.J. and Cyclin D1 amino acids 1-296; Ref. Cold Spring Harb. Symp. Quant. Biol., 1991; 56:93-97; Arnold A., Motokura T., Bloom T., Kronenburg, Ruderman J., Juppner H., Kim H.G.].

After sequencing the PCR products were cloned using standard techniques into the insect expression vector pVL1393 (obtained from Invitrogen 1995 catalogue number : V1392-20). The PCR products were then dually expressed [using a standard virus Baculogold co-infection technique] into the insect SF21 cell system (Spodoptera Frugiperda cells derived from ovarian tissue of the Fall Army Worm -Commercially available).

The following Example provides details of the production of Cyclin D1/CDK4 in SF21 cells (in TC100 + 10% FBS(TCS) + 0.2% Pluronic) having dual infection MOI 3 for each virus of Cyclin D1 & CDK4.

Example production of Cyclin D1/CDK4

SF21 cells grown in a roller bottle culture to 2.33 x 10^6 cells/ml were used to inoculate 10 x 500 ml roller bottles at 0.2 x 10E6 cells/ml. The roller bottles were incubated on a roller rig at 28°C.

After 3 days (72 hrs.) the cells were counted, and the average from 2 bottles found to be 1.86 x 10E6 cells/ml. (99% viable). The cultures were then infected with the dual viruses at an MOI 3 for each virus.

10 x 500ml were infected with JS303 Cyclin D1 virus titre - 9 x 10E7 pfu/ml. JS304 CDK4 virus titre - 1 x 10E8 pfu/ml.

Cyclin D1 $\frac{1.86 \times 10E6 \times 500 \times 3}{0.9 \times 10^8}$ = 31 ml of virus for each 500 ml. bottle.

CDK4 $\frac{1.86 \times 10E6 \times 500 \times 3}{1 \times 10^8}$ = 28 ml of virus for each 500 ml. bottle.

The viruses were mixed together before addition to the cultures, and the cultures returned to the roller rig 28°C.

After 3 days (72 hrs.) post infection the 5 Litres of culture was harvested. The total cell count at harvest was 1.58 x 10E6 cells/ml.(99% viable). The cells were spun out at 2500rpm, 30 mins., 4°C in Heraeus Omnifuge 2.0 RS in 250 ml lots. The supernatant was discarded. 20 pellets of ~ 4 x 10E8 cells/pellet were snap frozen in LN_2 and stored at -80°C in CCRF cold room. The SF21 cells were then hypotonically lysed by resuspending in lysis buffer (50mM HEPES pH 7.5, 10mM magnesium chloride, 1mM DTT, 10mM glycerophosphate, 0.1mM PMSF, 0.1mM sodium fluoride, 0.1mM sodium orthovanadate, 5ug/ml aprotinin, 5ug/ml leupeptin and 20% w/v sucrose), and adding ice cold deionised water. After centrifugation, the supernatant was loaded onto a Poros HQ/M 1.4/100 anion exchange column (PE Biosystems, Hertford, UK). CDK4 and Cyclin D1 were coeluted with 375mM NaCl in lysis buffer, and their presence checked by western blot, using suitable anti-CDK4 and anti-Cyclin D1 antibodies (obtained from Santa Cruz Biotechnology, California, US).

p16 control (Nature 366,:704-707; 1993; Serrano M, Hannon GJ, Beach D)

p16 (the natural inhibitor of CDK4/Cyclin D1) was amplified from HeLa cDNA (Hela cells obtained from ATCC CCL2, human epitheloid carcinoma from cervix; Cancer Res. 12: 264, 1952), cloned into pTB 375 NBSE which had a 5' His tag, and transformed using standard techniques into BL21 (DE3) pLysS cells (obtained from Promega; Ref. Studier F.W. and Moffat B.A., J. Mol. Biol., 189, 113, 1986). A 1 litre culture was grown to the appropriate OD then induced with IPTG to express p16 overnight. The cells were then lysed by sonication in 50mM sodium phosphate, 0.5M sodium chloride, PMSF, 0.5µg/ml leupeptin and 0.5µg/ml aprotinin. The mixture was spun down, the supernatant added to nickel chelate beads and mixed for 1 ½ hours. The beads were washed in sodium phosphate, NaCl pH 6.0 and p16 product eluted in sodium phosphate, NaCl pH 7.4 with 200mM imidazole.

The pTB NBSE was constructed from pTB 375 NBPE as follows :-

p TB375

The background vector used for generation of pTB 375 was pZEN0042 (see UK patent 2253852) and contained the tetA/tetR inducble tetracycline resistance sequence from plasmid RP4 and the cer stability sequence from plasmid pKS492 in a pAT153 derived background. pTB375 was generated by the addition of an expression cassette consisting of the T7 gene 10 promoter, multiple cloning site and T7 gene 10 termination sequence. In addition, a terminator sequence designed to reduce transcriptional readthrough from the background vector was included upstream of the expression cassette.

pTB 375 NBPE

The unique EcoRI restriction site present in pTB 375 was removed. A new multiple cloning site containing the recognition sequences for the restriction enzymes NdeI, BamHI, PstI and EcoRI was introduced into pTB 375 between the NdeI and BamHI sites destroying the original BamHI site present in pTB 375.

pTB 375 NBSE

A new multiple cloning site containing the recognition sequences for the restriction enzymes NdeI, BamHI, SmaI and EcoRI was introduced into pTB 375 NBPE between the NdeI and EcoRI sites. The oligonucleotide containing these restriction sites also contained 6 histidine codons located between the NdeI and BamHI sites in the same reading frame as the inititiator codon (ATG) present within the NdeI site.

By analogy to the above, assays designed to assess inhibition of CDK2 and CDK6 may be constructed. CDK2 (EMBL Accession No. X62071) may be used together with Cyclin A or Cyclin E (see EMBL Accession No. M73812), and further details for such assays are contained in PCT International Publication No. WO99/21845, the relevant Biochemical & Biological Evaluation sections of which are hereby incorporated by reference.

If using CDK2 with Cyclin E partial co-purification may be achieved as follows:- Sf21 cells are resuspended in lysis buffer (50mM Tris pH 8.2, 10mM $MgCl_2$, 1mM DTT, 10mM glycerophosphate, 0.1mM sodium orthovanadate, 0.1mM NaF, 1mM PMSF, 1ug/ml leupeptin and 1ug/ml aprotinin) and homogenised for 2 minutes in a 10ml Dounce homgeniser. After centrifugation, the supernatant is loaded onto a Poros HQ/M 1.4/100 anion exchange column (PE Biosystems, Hertford, UK). CDK2 and Cyclin E are coeluted at the

beginning of a 0-1M NaCl gradient (run in lysis buffer minus protease inhibitors) over 20 column volumes. Co-elution is checked by western blot using both anti-CDK2 and anti-Cyclin E antibodies (Santa Cruz Biotechnology, California, US).

FAK3 Kinase Inhibition Assay

This assay determines the ability of a test compound to inhibit tyrosine kinase activity of human Focal Adhesion Kinase (FAK).

DNA encoding FAK is obtained by total gene synthesis (Edwards M, International Biotechnology Lab 5(3), 19-25, 1987) or by cloning. These are then expressed in a suitable expression system to obtain polypeptide with tyrosine kinase activity. For example, FAK, obtained by expression of recombinant protein in insect cells, was found to display intrinsic tyrosine kinase activity.

FAK (full length human cDNA described by Andre et al (Biochemical and Biophysical Research Communications, 1993, 190 (1): 140-147; EMBL/GenBank Accession Number L05186)) was modified such that the resulting protein when translated had a 6-histidine tag at the N-terminus immediately preceding the start methionine. Active FAK protein has been previously expressed in a baculovirus system using a similar N-terminal 6-histidine tag (Protein Expression And Purification, 1996, 7: 12-18). The human FAK cDNA was cloned into the baculovirus transplacement vector, pFastbac 1 (Life Technologies), and the recombinant construct was co-transfected into insect cells (for example Spodoptera frugiperda 21(Sf21)) with viral DNA to prepare recombinant baculovirus (details of the methods for the assembly of recombinant DNA molecules and the preparation and use of recombinant baculovirus can be found in standard texts for example Sambrook et al, 1989, Molecular cloning - A Laboratory Manual, 2nd edition, Cold Spring Harbour Laboratory Press and O'Reilly et al, 1992, Baculovirus Expression Vectors - A Laboratory Manual, W. H. Freeman and Co, New York. Details specific to the use of the pFastbac ('Bac to Bac') system are provided in Anderson et al., 1995, FOCUS (Life Technologies Bulletin Magazine), 17, p53.)

For expression of biologically active human FAK protein, Sf21 cells were infected with plaque-pure FAK recombinant virus at a multiplicity of infection of 3 and harvested 48 hours later. Harvested cells were washed with ice cold phosphate buffered saline solution (PBS) (10mM sodium phosphate pH7.4, 138mM sodium chloride, 2.7mM potassium chloride) then resuspended in ice cold lysis buffer (50mM HEPES pH7.5, 1mM Dithiothreitol, 100uM Sodium Fluoride, 100uM Sodium Orthovanadate, 10mM Glycerophosphate, 100uM

Phenylmethylsulphonylfluoride (PMSF), 5ug/ml Aprotinin, 5ug/ml Leupeptin, 1% Tween; the PMSF being added just before use from a freshly-prepared 100mM solution in methanol) using 250µl lysis buffer per 10 million cells. The suspension was then incubated on ice for 15 minutes and centrifuged for 10 minutes at 13,000 rpm at 4°C. The supernatant (enzyme stock) was removed and aliquots made which were snap frozen in liquid nitrogen and then stored at -70°C. For a typical batch, stock enzyme was diluted 1 in 250 with enzyme diluent ((100mM HEPES pH 7.4, 0.2mM Dithiothreitol, 200uM Sodium Orthovanadate, 0.1% Triton X-100) and 50ml of freshly diluted enzyme was used for each assay well (see FAK3 protocol, below).

FAK3: *In vitro* Enzyme assay Protocol

A stock of substrate solution was prepared from a random copolymer containing tyrosine, for example Poly (Glu, Ala, Tyr) 6:3:1 (Sigma P3899), stored as 1 mg/ml stock in PBS at -20°C and diluted 1 in 500 with PBS for plate coating.

On the day before the assay 100µl of diluted substrate solution was dispensed into all wells of assay plates (Maxisorp 96 well immunoplates Life technologies, Cat. No. 439454A) which were sealed with plate sealers and left overnight at 4°C.

On the day of the assay the substrate solution was discarded and the assay plate wells were washed once with 200µl PBST (PBS containing 0.05% v/v Tween 20) and once with 200µl 50mM Hepes pH7.4.

Test compounds were made up as 10mM or 30mM stocks in DMSO and then further diluted in glass distilled water diluted to a concentration 10 fold higher than the final assay concentration. 10µl of diluted compound was transferred to wells in the washed assay plates. "No compound" control wells contained 10µl glass distilled water instead of compound.

Forty microlitres of 25mM manganese chloride containing 6.25µM adenosine-5'-triphosphate (ATP) was added to all test wells. To start the reactions 50µl of freshly diluted enzyme was added to each well and the plates were incubated at 23C for 90 minutes. Then the reaction was stopped by adding 100µl of PBS containing 20mM EDTA. The liquid was then discarded and the wells were washed twice with PBST.

One hundred microlitres of mouse HRP-linked anti-phosphotyrosine antibody (Santa Cruz, Product SC 7020-HRP), diluted 1 in 1500 with PBST containing 0.5% w/v bovine serum albumin (BSA), was added to each well and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with 200µl PBST. One hundred microlitres of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) solution,

freshly prepared using one 50mg ABTS tablet (Boehringer 1204 521) in 50ml freshly prepared 50mM phosphate-citrate buffer pH5.0 + 0.03% sodium perborate (made with 1 phosphate citrate buffer with sodium perborate (PCSB) capsule (Sigma P4922) per 100ml distilled water), was added to each well. Plates were then incubated for 20-60 minutes at room temperature until the absorbance value of the "no compound" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0.

Dose response curves were generated from the absorbance readings using Origin Software. Compounds were ranked for potency using the Inhibitory Concentration 50 (IC50), as defined by Origin Software analysis.

Although the pharmacological properties of the compounds of the formula **(I)** vary with structural change, in general activity possessed by compounds of the formula **(I)** in the above assays may be demonstrated at IC_{50} concentrations or doses in the range 250 μM to 1nM.

When tested in the above *in vitro* assay the CDK4 inhibitory activity of Example 13 was measured as IC_{50} = 0.896μM. When tested in the above *in vitro* assay the FAK inhibitory activity of Example 14 was measured as IC_{50} = 0.366μM.

The *in vivo* activity of the compounds of the present invention may be assessed by standard techniques, for example by measuring inhibition of cell growth and assessing cytotoxicity. For example, further details may be found in the following references:-

a) Attenution of the Expression of the Focal Adhesion Kinase induces Apoptosis in Tumor Cells. Xu L-h et al. Cell Growth & Differentiation (1996) 7, p413-418;

b) The COOH-Terminal Domain of the Focal Adhesion Kinase Induces Loss of Adhesion and Cell Death in Human Tumour Cells. Xu L-h et al. Cell Growth & Differentiation (1998) 9, p999-1005;

c) Inhibition of pp125-FAK in Cultured Fibroblasts Results in Apoptosis. Hungerford J.E et al. The Journal of Cell Biology (1996) 135, p1383-1390;

d) Inhibition of Focal Adhesion Kinase (FAK) Signalling in Focal Adhesions Decreases Cell Motility and Proliferation. Gilmore A.P and Romer L.H. Molecular Biology of the Cell (1996) 7, p1209-1224.

Inhibition of cell growth may be measured by staining cells with Sulforhodamine B (SRB), a fluorescent dye that stains proteins and therefore gives an estimation of amount of protein (i.e. cells) in a well (see Boyd, M. R. (1989) Status of the NCI preclinical antitumour

drug discovery screen. Prin. Prac Oncol 10:1-12). Thus, the following details are provided of measuring inhibition of cell growth:-

Cells were plated in appropriate medium in a volume of 100µl in 96 well plates; media was Dulbecco's Modified Eagle media for MCF-7, SK-UT-1B and SK-UT-1. The cells were allowed to attach overnight, then inhibitor compounds were added at various concentrations in a maximum concentration of 1% DMSO (v/v). A control plate was assayed to give a value for cells before dosing. Cells were incubated at 37°C, (5% CO2) for three days.

At the end of three days TCA was added to the plates to a final concentration of 16% (v/v). Plates were then incubated at 4°C for 1 hour, the supernatant removed and the plates washed in tap water. After drying, 100µl SRB dye (0.4% SRB in 1% acetic acid) was added for 30 minutes at 37°C. Excess SRB was removed and the plates washed in 1% acetic acid. The SRB bound to protein was solubilised in 10mM Tris pH7.5 and shaken for 30 minutes at room temperature. The ODs were read at 540nm, and the concentration of inhibitor causing 50% inhibition of growth was determined from a semi-log plot of inhibitor concentration versus absorbance. The concentration of compound that reduced the optical density to below that obtained when the cells were plated at the start of the experiment gave the value for toxicity.

Typical IC_{50} values for compounds of the invention when tested in the SRB assay are in the range 1mM to 1nM.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a pyrimidine derivative of the formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The pyrimidine will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form

such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a pyrimidine derivative of the formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

We have found that the pyrimidine derivatives defined in the present invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are effective cell cycle inhibitors (anti-cell proliferation agents), which property (without being bound by theory) is believed to arise from their CDK inhibitory properties. The compounds are also effective inhibitors of FAK. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by CDK and/or FAK enzymes, i.e. the compounds may be used to produce a CDK and/or FAK inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for treating the proliferation and/or migration of malignant cells characterised by inhibition of CDK and/or FAK enzymes, i.e. the compounds may be used to produce an anti-proliferative/migration effect mediated alone or in part by the inhibition of CDKs and/or FAK. The compounds may also be useful as FAK inhibitors by inducing cell-death (apoptosis). Such a pyrimidine derivative of the invention is expected to possess a wide range of anti-cancer properties as CDKs and/or FAK have been implicated in many common human cancers such as leukaemia and breast, lung, colon, rectal, stomach, prostate, bladder, pancreas and ovarian cancer. Thus it is expected that a pyrimidine derivative of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a pyrimidine derivative of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention, or a pharmaceutically acceptable salt or *in vivo*

hydrolysable ester thereof, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with CDK and/or FAK, especially those tumours which are significantly dependent on CDK and/or FAK for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

It is further expected that a pyrimidine derivative of the present invention will possess activity against other cell-proliferation/migration diseases in a wide range of other disease states including leukemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Thus according to this aspect of the invention there is provided a pyrimidine derivative of the formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use as a medicament; and the use of a pyrimidine derivative of the formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-cancer, cell cycle inhibitory (anti-cell-proliferation) effect and/or a FAK inhibitory (anti-cell migration and/or apoptosis inducing) effect in a warm-blooded animal such as man. Particularly, a cell cycle inhibitory effect is produced at the S or G1-S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK4 and CDK6.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-cancer, cell cycle inhibitory (anti-cell-proliferation) effect and/or a FAK inhibitory (anti-cell migration and/or apoptosis inducing) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a pyrimidine derivative as defined immediately above. Particularly, an inhibitory effect is produced at the S or G1-S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK4 and CDK6.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

The CDK and/or FAK inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other

substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the cell cycle inhibitory treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) other cell cycle inhibitory agents that work by the same or different mechanisms from those defined hereinbefore;

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincrisitine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan). According to this aspect of the invention there is provided a pharmaceutical product comprising a pyrimidine derivative of the formula **(I)** as defined hereinbefore, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, and

an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer. An anti-emetic may also be usefully administered, for example when using such conjoint treatment as described above.

In addition to their use in therapeutic medicine, the compounds of formula **(I)** and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other, pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

The invention will now be illustrated in the following non limiting Examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these Examples may be used where appropriate, and in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in vacuo and work up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, typically in the range 18-25°C and in air unless stated, or unless the skilled person would otherwise operate under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or on Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica, obtained from E. Merck, Darmstadt, Germany; bond elute chromatography was performed using Varian Mega Bond Elut cartridges (10 g, order code 1225-6034), obtained from Varian Sample Preparation Products, California, USA;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structures of the end products of the formula **(I)** were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured in deuterated DMSO-d_6 (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane) using a Varian Gemini 2000 spectrometer operating at a field strength of 300MHz, or a Bruker AM250 spectrometer operating at a field strength of 250MHz; and peak multiplicities are shown as follows: s,

singlet; d, doublet; dd, double doublet; t, triplet; tt, triple triplet; q, quartet; tq, triple quartet; m, multiplet; br, broad; mass spectrometry (MS) was performed by electrospray on a VG platform;

(vi) Analytical high performance liquid chromatography (HPLC) was performed on a Hypersil 10 cm base deactivated reverse phase column, at a flow rate of 2 ml/minute using 5-95% acetonitrile/water gradient over 10 minutes, detection was at a wavelength of 254 nm, and data are quoted as retention time (RT) in minutes;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis;

(viii) where solutions are dried magnesium sulphate was the drying agent;

(ix) the following abbreviations may be used hereinbefore or hereinafter:-

DCM	dichloromethane;
DMF	*N,N*-dimethylformamide;
DMSO	dimethylsulphoxide;
NMP	*N*-methylpyrrolidin-2-one;
THF	tetrahydrofuran.

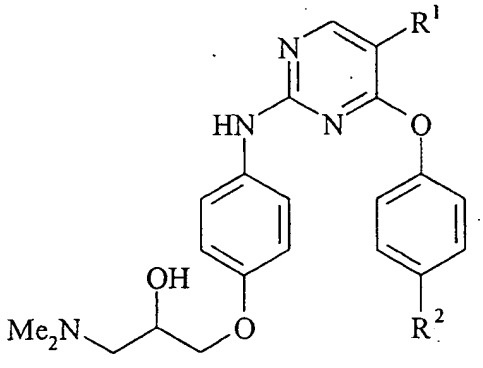
Example 1

5-Bromo-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}-4-(4-methoxyphenoxy) pyrimidine

A solution of 5-bromo-2-chloro-4-(4-methoxyphenoxy)pyrimidine (Method 1, 200 mg, 0.63 mmol) and 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride (Method 8, 156 mg, 0.56 mmol) in NMP (4 ml) was heated at 100°C for 6 hours. Silica (1 g) was added and volatile material was removed by evaporation. The residue was purified by column chromatography, eluting with 0-10% 2.0M methanolic ammonia solution in DCM, to give the product as a colourless solid (173 mg, 56%). MS (MH^+): 489, 491; HPLC (RT): 4.68.

Examples 2-4

The following compounds were prepared by an analogous method to that described in Example 1, using 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride (Method 8) and the appropriate 4,5-disubstituted 2-chloropyrimidine (Methods 2-4):



Ex	R^1	R^2	NMR	MS (MH^+)
2[1]	Br	H	2.80 (dd, 6H), 3.1-3.25 (m, 2H), 3.85 (m, 2H), 4.25 (m, 1H), 6.63 (d, 2H), 7.2-7.3 (m, 4H), 7.33 (t, 1H), 7.49 (t, 2H), 8.45 (s, 1H), 9.57 (br s, 1H), 9.80 (br s, 1H)	459.3, 461.3
3	Cl	OMe	2.17 (s, 6H), 2.2-2.4 (m, 2H), 3.7-3.9 (m, 6H), 4.75 (br s, 1H), 6.62 (d, 2H), 7.02 (d, 2H), 7.18 (d, 2H), 7.24 (d, 2H), 8.35 (s, 1H), 9.47 (br s, 1H)	445, 447
4	F	OMe	2.17 (s, 6H), 2.20-2.40 (m, 2H), 3.64-3.90 (m, 6H), 4.68-4.77 (m, 1H), 6.63 (d, 2H), 7.02 (d, 2H), 7.18-7.34 (m, 4H), 8.38 (d, 1H), 9.28 (s, 1H)	429

[1] Reaction carried out in tetramethylene sulphone at 150°C and product isolated as dihydrochloride salt by dilution of reaction mixture with DCM and addition of ethereal hydrogen chloride.

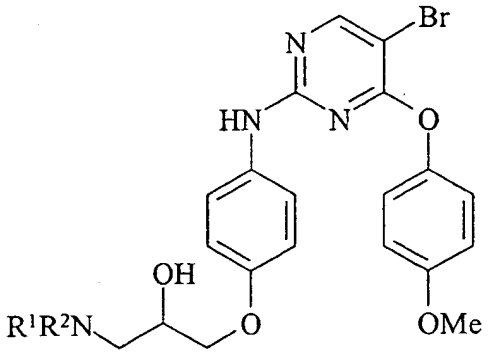
Example 5

5-Bromo-2-{4-[3-(isobutylamino)-2-hydroxypropoxy]anilino}-4-(4-methoxyphenoxy) pyrimidine

Ethereal hydrogen chloride (2.0M; 0.57 ml, 1.14 mmol) was added to a solution of 5-bromo-2-chloro-4-(4-methoxyphenoxy)pyrimidine (Method 1, 200 mg, 0.63 mmol) and 4-[3-(isobutylamino)-2-hydroxypropoxy]aniline (Method 10, 136 mg, 0.57 mmol) in NMP (4 ml). The solution was heated at 100°C for 6 hours and silica (1 g) was added. Volatile material was removed by evaporation and the residue was purified by column chromatography, eluting with 0-10% 2.0M methanolic ammonia solution in DCM, to give the product as a colourless solid (76 mg, 26%). MS (MH^+): 517, 519; HPLC (RT): 6.48.

Examples 6-10

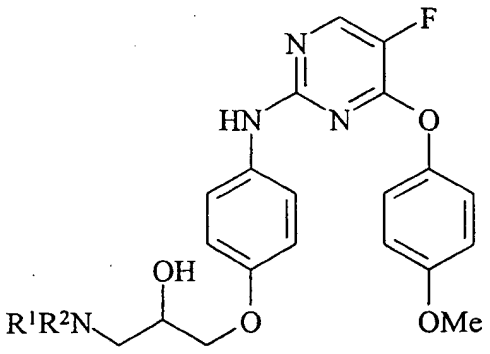
The following compounds were prepared by an analogous method to that described in Example 5, using 5-bromo-2-chloro-4-(4-methoxyphenoxy)pyrimidine (Method 4) and the appropriate substituted aniline (Methods 11-15):



Ex	R^1	R^2	MS (MH^+)	HPLC (RT)
6	cyclopentyl	H	529, 531	6.48
7	pyrrolidino		515, 517	6.79
8	Me	H	475, 477	4.30
9	H	H	461, 463	3.59
10	Et	H	489, 491	4.84

Examples 11-13

The following compounds were prepared by an analogous method to that described in Example 5, using 2-chloro-5-fluoro-4-(4-methoxyphenoxy)pyrimidine (Method 4) and the appropriate substituted aniline (Methods 11, 16 or obtained as described in Pharmazie, 1980, 35, 278):



Ex	R^1	R^2	NMR	MS (MH^+)
11	4-acetylpiperazin-1-yl		1.96 (s, 3H), 2.27-2.55 (m, 6H), 3.32-3.45 (m, 4H), 3.70-3.98 (m, 6H), 4.82 (d, 1H), 6.35 (d, 2H), 7.03 (d, 2H), 7.12 (d, 2H), 7.30 (d, 2H), 8.37 (d, 1H), 9.30 (s, 1H)	512
12	cyclopentyl	H	1.17-1.78 (m, 8H), 2.40-2.66 (m, 2H), 2.98 (m, 1H), 3.69-3.89 (m, 6H), 4.86 (br s, 1H), 6.63 (d, 2H), 7.03 (d, 2H), 7.11 (d, 2H), 7.30 (d, 2H), 8.38 (d, 1H), 9.29 (s, 1H)	469
13	*i*-Pr	H	0.98 (d, 6H), 1.47 (br s, 1H), 2.44-2.75 (m, 3H), 3.68-3.89 (m, 6H), 4.90 (br s, 1H), 6.63 (d, 2H), 7.03 (d, 2H), 7.16-7.25 (m, 4H), 8.38 (d, 1H), 9.39 (s, 1H)	443

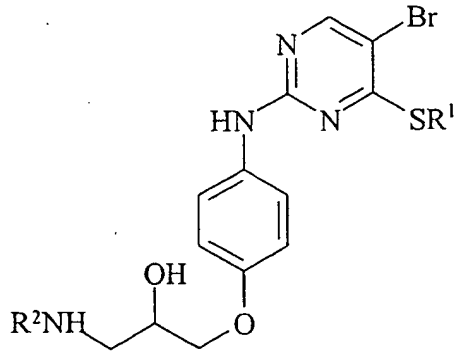
Example 14

5-Bromo-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}-4-(phenylthio)pyrimidine

Using an analogous method to that described in Example 1, but starting from 5-bromo-2-chloro-4-(phenylthio)pyrimidine (Method 6) and 4-[2-hydroxy-3-(*N,N*-dimethylamino) propoxy]aniline hydrochloride (Method 8), the product was obtained. NMR: 2.2 (s, 6H), 2.3 (m, 2H), 3.7 (m, 1H), 3.9 (m, 2H), 4.7 (d, 1H), 6.5 (d, 2H), 7.0 (d, 2H), 7.6 (5H), 8.3 (s, 1H), 9.5 (s, 1H); MS (MH^+): 475, 477.

Examples 15-17

The following compounds were prepared by an analogous method to that described in Example 5, using the appropriate 4-substituted 5-bromo-2-chloropyrimidine (Methods 6-7) and the appropriate substituted aniline (obtained as described in Pharmazie, 1980, 35, 278):



Ex	R^1	R^2	NMR	MS (MH^+)
15	Ph	i-Pr	0.95 (s, 3H), 1.0 (s, 3H), 2.5 (m, 1H), 2.7 (m, 2H), 3.8 (m, 3H), 4.9 (s, 1H), 6.5 (d, 2H), 7.0 (d, 2H), 7.6 (m, 5H), 8.3 (s, 1H), 9.5 (s, 1H)	489, 491
16	Ph	t-Bu	1.1 (s, 9H), 2.8 (m, 2H), 3.8 (m, 3H), 6.5 (d, 2H), 7.0 (d, 2H), 7.6 (m, 5H), 8.3 (s, 1H), 9.5 (s, 1H)	503, 505
17	thiazol-2-yl	i-Pr	1.10 (d, 6H), 2.72 (m, 1H), 2.80-2.95 (m, 2H), 3.85-4.05 (m, 3H), 6.62 (d, 2H), 7.02 (d, 2H), 7.65 (d, 1H), 8.03 (d, 1H), 8.16 (s, 1H)[1]	496, 498

[1] Recorded in $CDCl_3$

Preparation of Starting Materials:

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example, the following reactions are an illustration, but not a limitation, of some of the starting materials used in the above reactions.

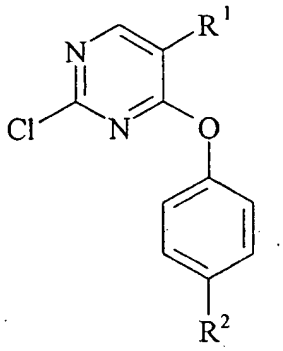
Method 1

5-Bromo-2-chloro-4-(4-methoxyphenoxy)pyrimidine

A mixture of 5-bromo-2,4-dichloropyrimidine (5.0 g, 22.0 mmol), 4-methoxyphenol (2.72 g, 22.0 mmol) and potassium carbonate (6.07 g, 44.0 mmol) in DMF (20 ml) was stirred for 24 hours. The mixture was added to water (100 ml) and the solid which separated out was collected by filtration, washed with water (50 ml) and dried under high vacuum to give the product (6.6 g, 96%). NMR: 3.8 (s, 3H), 7.0 (d, 2H), 7.2 (d, 2H), 8.8 (s, 1H).

Methods 2-4

The following intermediates were prepared by an analogous method to that described in Method 1, using the appropriate phenol and the appropriate 2,4-dichloro-5-halopyrimidine (commercially available or obtained as described in Method 5):



Method	R^1	R^2	MS (MH^+)
2	Br	H	285.1, 287.1
3	Cl	OMe	271, 273
4	F	OMe	254, 256

Method 5

2,4,5-Trichloropyrimidine

5-Chlorouracil (10.0 g, 68.5 mmol) was dissolved in phosphorus oxychloride (60 ml) and phosphorus pentachloride (16.0 g, 77.0 mmol) was added. The mixture was heated under reflux for 16 hours, left to cool and then poured slowly into water (200 ml) with vigorous stirring. The mixture was stirred for 1.5 hours and then ethyl acetate (250 ml) was added. The organic layer was separated and the aqueous layer was extracted with a further portion of ethyl acetate (250 ml). The combined extracts were washed with saturated sodium bicarbonate (200 ml) and saturated sodium chloride solution (200 ml), and then dried. Volatile material was removed by evaporation and the residue was purified by column chromatography, eluting with DCM, to give the product as a yellow liquid (6.37 g, 51%). NMR ($CDCl_3$): 8.62 (s, 1H); MS (MH^+): 182, 184, 186.

Method 6

5-Bromo-2-chloro-4-(phenylthio)pyrimidine

Using an analogous method to that described in Method 1, but starting from 5-bromo-2,4-dichloropyrimidine and thiophenol, the product was obtained. NMR: 7.6 (m, 5H), 8.8 (s, 1H).

Method 7

5-Bromo-2-chloro-4-(thiazolyl-2-ylthio)pyrimidine

A solution of 5-bromo-2,4-dichloropyrimidine (228 mg, 1.0 mmol), 2-mercaptothiazole (117 mg, 1.0 mmol) and *N,N*-diisopropylethylamine (0.174 ml, 1.0 mmol) in *n*-butanol (10 ml) was heated at 100°C for 2 hours. Volatile material was removed by evaporation and the residue was crystallised from methanol to give the product as colourless needles (130 mg, 42%). NMR ($CDCl_3$): 7.65 (d, 1H), 7.99 (d, 1H), 8.44 (s, 1H); MS (MH^+): 307.8, 309.8.

Method 8

4-[2-Hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride

A solution of 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]nitrobenzene (Method 9, 3.75 g) in ethanol (40 ml) was catalytically hydrogenated over 10% palladium-on-carbon (0.4 g) overnight. The catalyst was removed by filtration through diatomaceous earth and the filtrate was concentrated. The residue was dissolved in diethyl ether containing a small amount of isopropanol and ethereal hydrogen chloride (1M, 16 ml) was added. Diethyl ether was removed by evaporation and the solid residue was suspended in isopropanol. The mixture was heated on a steam bath for several minutes and then allowed to cool. The insoluble solid was collected by filtration, washed with isopropanol and ether, and dried to give the product (3.04 g, 72.4%). NMR: 2.80 (s, 6H), 3.15 (m, 2H), 3.88 (m, 2H), 4.25 (m,1H), 5.93 (br S, 1H), 6.88 (m, 4H); MS (MH^+): 211; $C_{11}H_{18}N_2O_2.1.6$ HCl requires: C; 49.2, H; 7.4, N; 10.4, Cl; 21.7%; found: C; 49.2, H; 7.2, N; 10.1; Cl; 19.1%.

Method 9

4-[2-Hydroxy-3-(*N,N*-dimethylamino)propoxy]nitrobenzene

4-(2,3-Epoxypropoxy)nitrobenzene (obtained as described in Synthetic Communications, 1994, 24, 833; 4.3 g) was dissolved in methanol (30 ml) and DMF (10 ml). A solution of dimethylamine in methanol (2M, 17 ml) was added and the mixture was stirred overnight. Volatile material was removed by evaporation and the residue was partitioned between saturated sodium bicarbonate (100 ml) and ethyl acetate (100 ml). The organic layer was separated and washed with saturated sodium chloride (2 x 100 ml) and dried. Concentration gave the product as an oil that slowly crystallised under high vacuum (4.79 g, 89.9%). NMR ($CDCl_3$): 2.33 (s, 6H), 2.98 (m, 1H), 2.54 (m, 1H), 4.00 (m, 3 H), 7.00 (d, 2H), 8.20 (d, 2H); MS (MH^+): 241.

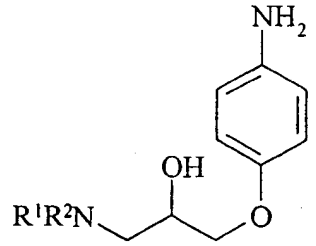
Method 10

4-[3-(Isobutylamino)-2-hydroxypropoxy]aniline

Isobutylamine (5.1 ml, 51.2 mmol) was added to a solution of 4-(2,3-epoxypropoxy) nitrobenzene (obtained as described in Synthetic Communications, 1994, 24, 833; 1.0 g, 5.12 mmol) in THF (1 ml). The solution was heated under reflux for 3 hours and then volatile material was removed by evaporation. The residue was dissolved in methanol (5 ml) and 10% palladium on carbon (0.50 g) and ammonium formate (3.23 g, 51.2 mmol) were added. The mixture was heated under reflux for 3 hours and then filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure to give the product as dark brown oil (1.22 g, 100%), which was used without further purification. MS (MH^+): 238.9.

Methods 11-16

The following intermediates were prepared by an analogous method to that described in Method 10, using 4-(2,3-epoxypropoxy)nitrobenzene (obtained as described in Synthetic Communications, 1994, 24, 833) and the appropriate amine.



Method	R^1	R^2	MS (MH^+)
11	cyclopentyl	H	250.9
12	pyrrolidino		236.9
13[1]	Me	H	196.9
14[1]	H	H	182.9
15[1]	Et	H	210.9
16	4-acetylpiperazin-1-yl		296.9

[1] Prepared from the corresponding *N*-benzyl substituted precursors. For complete de-benzylation, the reactions required a further addition of 10% palladium on carbon (0.50 g) and ammonium formate (3.23 g).

Example 18

The following illustrate representative pharmaceutical dosage forms containing the compound of formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

(a): Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c): Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d): Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e): Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	(to adjust pH to 7.6)
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f): Injection II	10 mg/ml
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

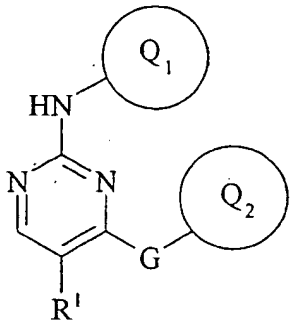
(g): Injection III	**(1mg/ml, buffered to pH6)**
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

Claims

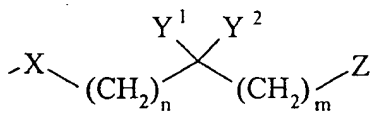
1. A pyrimidine derivative of the formula **(I)**:



(I)

wherein:

$\mathbf{Q_1}$ and $\mathbf{Q_2}$ are independently selected from aryl or carbon linked heteroaryl; and one of Q_1 and Q_2 or both of Q_1 and Q_2 is substituted on a ring carbon by one substituent of the formula **(Ia)**:



(Ia)

[provided that when present in Q_1 the substituent of formula **(Ia)** is not adjacent to the -NH- link];

wherein:

X is $-CH_2-$, -O-, -NH-, $-NR^a-$ or -S- [wherein R^a is C_{1-4}alkyl, optionally substituted by one substituent selected from halo, amino, cyano, C_{1-4}alkoxy or hydroxy];

$\mathbf{Y^1}$ is H, C_{1-4}alkyl or as defined for Z;

$\mathbf{Y^2}$ is H or C_{1-4}alkyl;

Z is R^bO-, R^cR^dN-, R^eS-, $R^fR^gNNR^h-$, a nitrogen linked heteroaryl or a nitrogen linked heterocycle [wherein said heterocycle is optionally substituted on a ring carbon or a ring nitrogen by C_{1-4}alkyl or C_{1-4}alkanoyl] wherein R^b, R^c, R^d, R^e, R^f, R^g and R^h are independently selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{3-8}cycloalkyl, and wherein said C_{1-4}alkyl and C_{2-4}alkenyl are optionally substituted by one or more phenyl;

n is 1, 2 or 3;

m is 1, 2 or 3;

G is -O- or -S-;

R^1 is selected from hydrogen, halo, hydroxy, nitro, amino, *N*-(C_{1-3}alkyl)amino, *N*,*N*-di-(C_{1-3}alkyl)amino, cyano, trifluoromethyl, trichloromethyl, C_{1-3}alkyl [optionally substituted by 1 or 2 substituents independently selected from halo, cyano, amino, *N*-(C_{1-3}alkyl)amino, *N*,*N*-di-(C_{1-3}alkyl)amino, hydroxy and trifluoromethyl], C_{3-5}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{3-5}alkynyl, C_{1-3}alkoxy, mercapto, C_{1-3}alkylsulphanyl, carboxy and C_{1-3}alkoxycarbonyl;

Q_1 is optionally substituted on a ring carbon by one to four substituents independently selected from halo, mercapto, nitro, formyl, formamido, carboxy, cyano, amino, ureido, carbamoyl, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl [wherein said C_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl are optionally substituted by one or more groups selected from R^i], C_{1-4}alkanoyl, C_{1-4}alkoxycarbonyl, heterocyclic group, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 [optionally substituted by hydroxy], *N'*-(C_{1-4}alkyl)ureido, *N'*,*N'*-di-(C_{1-4}alkyl)ureido, *N'*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N'*,*N'*-di-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N*-C_{1-4}alkylamino, *N*,*N*-di-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N*,*N*-di-(C_{1-4}alkyl)sulphamoyl, *N*-C_{1-4}alkylcarbamoyl, *N*,*N*-di-(C_{1-4}alkyl)carbamoyl and C_{1-4}alkanoylamino;

and also independently, or in addition to, the above substituents, Q_1 may be optionally substituted by one to two substituents independently selected from aryl, C_{3-8}cycloalkyl and a heterocyclic group; wherein said aryl, C_{3-8}cycloalkyl or heterocyclic group may be optionally substituted on a ring carbon by one or more groups selected from R^j; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^k;

Q_2 is optionally substituted on a ring carbon by one to four substituents independently selected from halo, hydroxy, mercapto, nitro, formyl, formamido, carboxy, cyano, amino, ureido, carbamoyl, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy [wherein said C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl and C_{1-4}alkoxy are optionally substituted by one or more groups selected from R^l], C_{1-4}alkanoyl, C_{1-4}alkoxycarbonyl, heterocyclic group, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 [optionally substituted by hydroxy], *N'*-(C_{1-4}alkyl)ureido, *N'*,*N'*-di-(C_{1-4}alkyl)ureido, *N'*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N'*,*N'*-di-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N*-C_{1-4}alkylamino, *N*,*N*-di-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N*,*N*-di-(C_{1-4}alkyl)sulphamoyl, *N*-C_{1-4}alkylcarbamoyl,

N,*N*-di-(C_{1-4}alkyl)carbamoyl, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, C_{1-4}alkanoylamino and a group of formula **(Ia)** or **(Ia')** as depicted above;

and also independently, or in addition to, the above substituents, Q_2 may be optionally substituted by one to two substituents independently selected from aryl, C_{3-8}cycloalkyl or a heterocyclic group; wherein said aryl, C_{3-8}cycloalkyl or heterocyclic group may be optionally substituted on a ring carbon by one or more groups selected from R^m; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^n;

$\mathbf{R^l}$ and $\mathbf{R^l}$ are independently selected from hydroxy, halo, amino, cyano, formyl, formamido, carboxy, nitro, mercapto, carbamoyl, sulphamoyl, *N*-C_{1-4}alkylamino, *N*,*N*-di-(C_{1-4}alkyl)amino, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, *N*-C_{1-4}alkylcarbamoyl, *N*,*N*-di-(C_{1-4}alkyl)carbamoyl, C_{1-4}alkanoylamino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkylsulphonylamino, *N*-(C_{1-4}alkyl)sulphamoyl, *N*-(C_{1-4}alkyl)$_2$sulphamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N*-(C_{1-4}alkyl)$_2$carbamoyl, phenyl, phenylthio, phenoxy, C_{3-8}cycloalkyl and a heterocyclic group; wherein said phenyl, phenylthio, phenoxy, C_{3-8}cycloalkyl or heterocyclic group may be optionally substituted on a ring carbon by one or more groups selected from R^o; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^p;

$\mathbf{R^j}$, $\mathbf{R^m}$ and $\mathbf{R^o}$ are independently selected from hydroxy, halo, amino, cyano, formyl, formamido, carboxy, nitro, mercapto, carbamoyl, sulphamoyl, C_{1-4}alkyl [optionally substituted by one or more groups selected from halo, cyano, amino, *N*-C_{1-4}alkylamino, *N*,*N*-di-(C_{1-4}alkyl)amino or hydroxy], C_{2-4}alkenyl [optionally substituted by one or more groups selected from halo], C_{2-4}alkynyl, *N*-C_{1-4}alkylamino, *N*,*N*-di-(C_{1-4}alkyl)amino, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, C_{1-4}alkoxy [optionally substituted by one or more groups selected from halo], C_{1-4}alkoxycarbonyl, *N*-C_{1-4}alkylcarbamoyl, *N*,*N*-di-(C_{1-4}alkyl)carbamoyl, C_{1-4}alkanoylamino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkylsulphonylamino, *N*-(C_{1-4}alkyl)sulphamoyl, *N*-(C_{1-4}alkyl)$_2$sulphamoyl, phenyl, C_{3-8}cycloalkyl and a heterocyclic group; and

$\mathbf{R^k}$, $\mathbf{R^n}$ and $\mathbf{R^p}$ are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N*,*N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

2. A pyrimidine derivative according to claim 1 wherein Q_1 is phenyl or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

3. A pyrimidine derivative according to either of claims 1 or 2 wherein Q_2 is phenyl or thiazolyl or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

4. A pyrimidine derivative according to any one of claims 1 to 3 wherein the substituent **(Ia)** is 3-amino-2-hydroxypropoxy, 3-methylamino-2-hydroxypropoxy, 3-dimethylamino-2-hydroxypropoxy, 3-ethylamino-2-hydroxypropoxy, 3-isopropylamino-2-hydroxypropoxy, 3-isobutylamino-2-hydroxypropoxy, 3-*t*-butylamino-2-hydroxypropoxy, 3-(4-acetylpiperazin-1-yl)-2-hydroxypropoxy, 3-cyclopentylamino-2-hydroxypropoxy or 3-pyrrolidin-1-yl-2-hydroxypropoxy or thiazolyl or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

5. A pyrimidine derivative according to any one of claims 1 to 4 wherein the substituent of formula **(Ia)** is on ring Q_1 or thiazolyl or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

6. A pyrimidine derivative according to any one of claims 1 to 5 wherein G is -O- or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

7. A pyrimidine derivative according to any one of claims 1 to 5 wherein G is -S- or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

8. A pyrimidine derivative according to any one of claims 1 to 7 wherein R^1 is fluoro, chloro or bromo or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

9. A pyrimidine derivative according to any one of claims 1 to 8 wherein Q_2 is unsubstituted or substituted by one methoxy group or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

10. A pyrimidine derivative according to any one of claims 1 to 9 selected from:

5-bromo-2-{4-[2-hydroxy-3-(*N*,*N*-dimethylamino)propoxy]anilino}-4-(4-methoxyphenoxy) pyrimidine;

5-bromo-2-{4-[2-hydroxy-3-(cyclopentylamino)propoxy]anilino}-4-(4-methoxyphenoxy) pyrimidine;

5-bromo-2-{4-[2-hydroxy-3-(*N*,*N*-dimethylamino)propoxy]anilino}-4-(phenylthio)pyrimidine;

5-bromo-2-{4-[2-hydroxy-3-(isopropylamino)propoxy]anilino}-4-(phenylthio)pyrimidine;

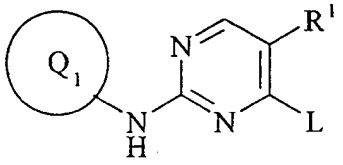
5-bromo-2-{4-[2-hydroxy-3-(*t*-butylamino)propoxy]anilino}-4-(phenylthio)pyrimidine; or

5-bromo-2-{4-[2-hydroxy-3-(isopropylamino)propoxy]anilino}-4-(thiazol-2-ylthio)pyrimidine;

or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

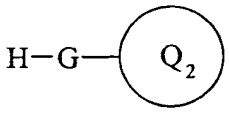
11. A process for preparing a pyrimidine derivative according to any one of claims 1 to 10 selected from:

a) for compounds of formula **(I)**; reacting a pyrimidine of formula **(II)**:



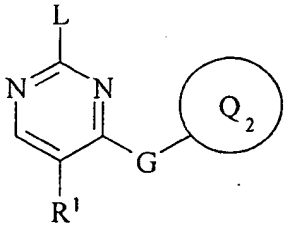
(II)

wherein L is a displaceable group as defined below, with a compound of formula **(III)**:



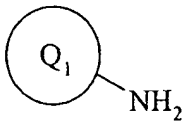
(III)

b) reaction of a pyrimidine of formula **(IV)**:



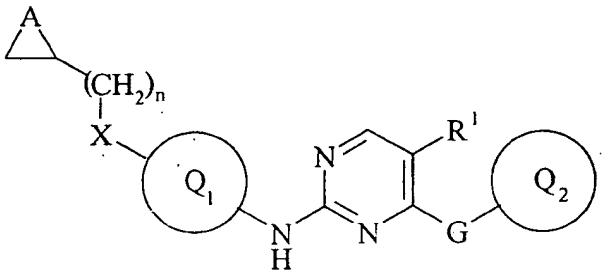
(IV)

wherein L is a displaceable group as defined below, with a compound of formula **(V)**:



(V)

c) for compounds of formula **(I)** where n is 1, 2 or 3, m = 1, Y^2 is H and Y^1 is OH, NH_2 or SH; by reaction of a 3-membered heteroalkyl ring of formula **(VI)**:



(VI)

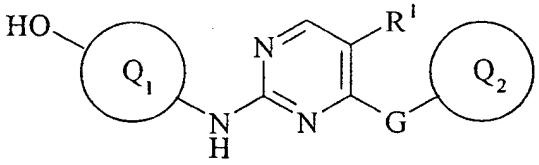
wherein A is O, S or NH; with a nucleophile of formula **(VII)**:

Z-D

(VII)

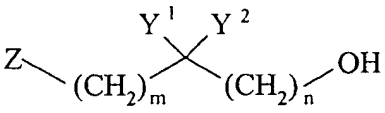
wherein D is H or a suitable counter-ion;

d) for compounds of formula **(I)** where X is oxygen; by reaction of an alcohol of formula **(VIII)**:



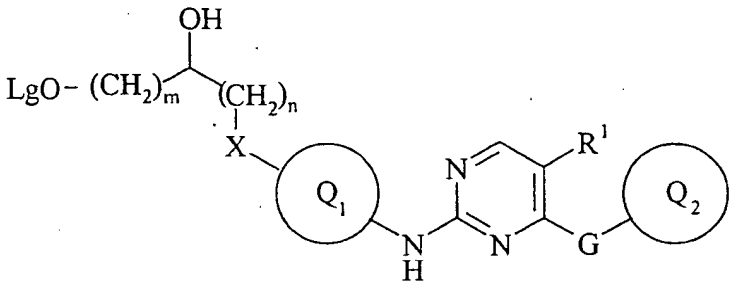
(VIII)

with an alcohol of formula **(IX)**:



(IX)

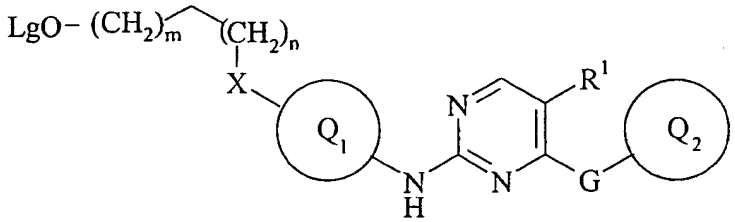
e) for compounds of formula **(I)** wherein X is $-CH_2-$, -O-, -NH- or -S-, Y^1 is OH, Y^2 is H and m is 2 or 3; reaction of a compound of formula **(X)**:



(X)

wherein LgO is a leaving group as defined below; with a nucleophile of formula **(VII)**;

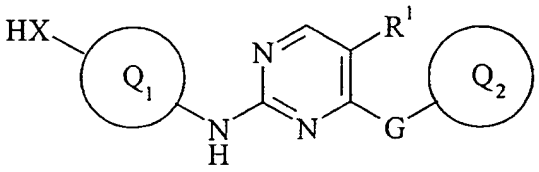
f) for compounds of formula **(I)** wherein X is $-CH_2-$, -O-, -NH- or -S-; Y^1 and Y^2 are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula **(XI)**:



(XI)

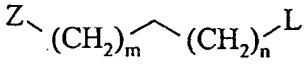
wherein LgO is a leaving group as defined below; with a nucleophile of formula **(VII)**;

g) for compounds of formula **(I)** wherein X is -O-, -NH- or -S-; Y^1 and Y^2 are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula **(XII)**:



(XII)

with a compound of formula **(XIII)**



(XIII)

wherein L is a displaceable group as defined below;

h) for compounds of formula **(I)** in which Z is HS-, by conversion of a thioacetate group in a corresponding compound;

and thereafter if necessary:

i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

12. A pharmaceutical composition which comprises a pyrimidine derivative of the formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 to 10, in association with a pharmaceutically acceptable diluent or carrier.

13. A pyrimidine derivative of the formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 to 10, for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

14. A pyrimidine derivative of the formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 to 10, for use as a medicament.

15. The use of a pyrimidine derivative of the formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 to 10, in the manufacture of a medicament for use in the production of an anti-cancer, cell cycle inhibitory (anti-cell-proliferation) effect and/or a FAK inhibitory (anti-cell migration and/or apoptosis inducing) effect in a warm-blooded animal such as man.

16. A method for producing an anti-cancer, cell cycle inhibitory (anti-cell-proliferation) effect and/or a FAK inhibitory (anti-cell migration and/or apoptosis inducing) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a pyrimidine derivative as claimed in any one of claims 1 to 10, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/00794

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/46 C07D417/12 A61K31/505 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 41512 A (CELLTECH THERAP.) 24 September 1998 (1998-09-24) page 0; claims; examples 2,12,13,18	1,2, 11-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 July 2001	12/07/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 01/00794

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9841512 A	24-09-1998	AU 6411698 A	12-10-1998
		EP 0970056 A	12-01-2000
		US 6048866 A	11-04-2000